THE CHEMISTRY OF THE HYDANTOINS

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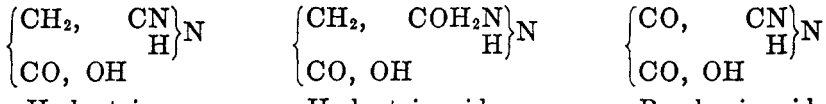
I. INTRODUCTION

A. Discovery and structure of hydantoin

Hydantoin was discovered in 1861 by Baeyer, who isolated it as one of the reduction products of allantoin during the course of his now classic study of uric acid (25). The new substance was named "hydantoin," since it had been obtained

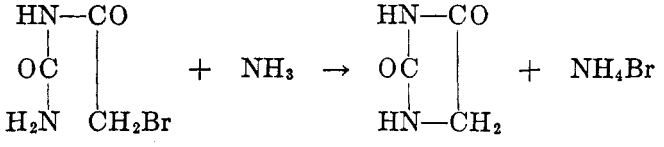
through the reduction, or hydrogenation, of allantoin. In the same year, Baeyer reported that hydantoin could also be obtained by reducing alloxanic acid with hydrogen iodide (26), and three years later succeeded in synthesizing hydantoin from bromoacetylurea (27). While Baeyer classified hydantoin as a member of the same group of substances as parabanic acid, calling parabanic acid "oxalyl urea" and hydantoin "glycolyl urea," its configuration was not clarified until 1870. Baeyer also observed that hydantoin was converted into the barium salt of a carboxylic acid when boiled with a dilute aqueous solution of barium hydroxide (27); this acid, called "hydantoic acid," together with a number of its salts, was studied by Baeyer and by Herzog (328).

The first structural formulae for hydantoic acid, hydantoin, and parabanic acid were suggested in 1870 by Kolbe (405, 406):

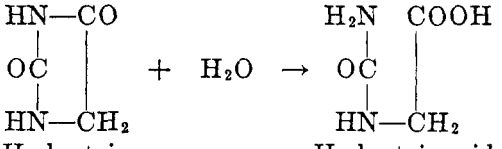


Hydantoin, or cyamido-acetic acid | Hydantoic acid, or uramido-acetic acid | Parabanic acid

These formulae were almost immediately criticized by Strecker (587), who proposed the structures now accepted for hydantoin and for hydantoic acid, and who also showed that the synthesis of hydantoin from bromoacetylurea under the action of alcoholic ammonia could best be explained by the cyclic ureide representation of hydantoin.



Since hydantoic acid contains two hydrogen atoms and one oxygen atom more than hydantoin, it was assumed by Strecker to result from a cleavage of the hydantoin ring and the simultaneous addition of a molecule of water:



Hydantoin | Hydantoic acid

Several systems for designating the positions in the hydantoin ring have been used. Here a certain amount of confusion is to be encountered in the literature because a difference in usage exists (*a*) prior to 1907 and (*b*) following the year 1907:

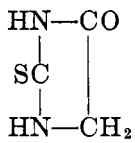
(a) | (b)

The latter system is the one which has been accepted by the editors of *Chemical Abstracts* and which will be followed in the present paper, but the reader should bear in mind that names different from those employed may be met with in the original reports to which reference will be made; not only these two systems but also others have been used at various times. While hydantoin may also be called 2,4-imidazoledione or 2,4-diketotetrahydroimidazole, the name "hydantoin" will be used in this paper.

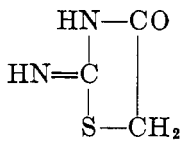
B. THIOHYDANTOINS AND PSEUDOTHIOHYDANTOINS

Closely allied to the hydantoins are the 2-thiohydantoins. It has seemed desirable to consider these two types of compound more or less together, since they undergo analogous reactions in the presence of the same or of similar reagents. Moreover, 2-thiohydantoin and its various derivatives are readily converted into the corresponding oxygen compounds. This last statement is of particular importance, since the sulfur hydantoins are frequently not only prepared and isolated more easily than the oxygen compounds, but are also more reactive. A few 4-thiohydantoins and 2,4-dithiohydantoins have been prepared; these also have chemical properties similar to those of the corresponding oxygen compounds.

Pseudothiohydantoins are isomeric with 2-thiohydantoins:



2-Thiohydantoin



Pseudothiohydantoin

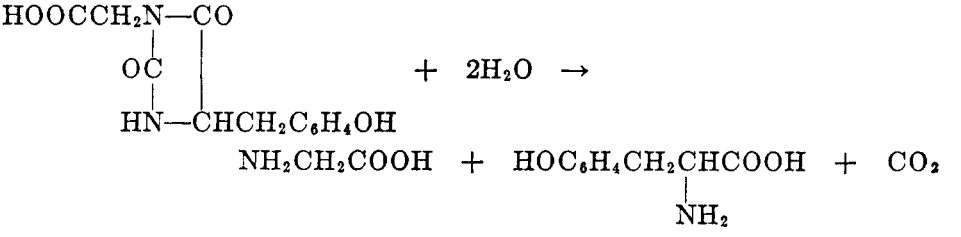
This class of compounds is mentioned only because there has been some confusion in the literature, even recent papers (201, 514) referring to compounds as 2-thiohydantoins when they have been prepared by methods known to lead to the formation of pseudothiohydantoins, and no attempt will be made here to discuss their chemistry in detail. The difference between 2-thiohydantoins and pseudothiohydantoins was first recognized in 1879 by Liebermann and Lange (425, 426); further study of the structural differences was made by Aschan (21) and by Dixon (190). One of the principal methods of preparation of pseudothiohydantoins is through the interaction of a thiourea with chloroacetic acid; this reaction was studied by a number of investigators between 1873 and 1879, and was believed to lead to the formation of 2-thiohydantoins (242, 416, 453, 471, 473, 611, 612). It was soon found, however, that these compounds gave unexpected results when hydrolyzed (7), oxidized (9), or treated with metallic oxides in attempts to desulfurize them (611, 612). It was the hydrolysis of a diphenyl derivative of pseudothiohydantoin to form aniline and thioglycolic acid which led Liebermann and Lange to conclude that their "diphenyl thiohydantoin" had been incorrectly formulated (425).

C. Natural occurrence of hydantoins

Hydantoins have been isolated from a number of natural sources. Hydantoin has been found in the buds of the oriental plane tree (554) and in the white shoots

of sugar beets (434), while a methylated hydantoin was isolated from a testicular extract containing pressor substances (155). The presence of hydantoin nuclei has been indicated as probable in studies of the chemical nature of xanthopterin, present in the wing pigments of butterflies (633), and in gliotoxin (200). Although it has been reported that after the ingestion or intravenous injection of large amounts of amino acids, among them sarcosine (42, 553) and tyrosine (85), the hydantoic acids or hydantoins derived from these amino acids were present in the urine, the work of Dakin indicates that the methods of isolation may have brought about their formation as a result of the combination of the amino acids with urea (167, 169). A similar conclusion was reached by Hoppe-Seyler as a result of his study of lysine excretion (337).

Hydantoins may be regarded as the cyclic ureides of α-amino acids, and these two types of compound are readily interconvertible, as will be shown in later sections of this paper. In view of this close relationship between hydantoins and α-amino acids, it was suggested by Lippich that hydantoic acids (433) and by T. B. Johnson that hydantoins (358) might be present in proteins. It was pointed out by Johnson that the production of approximately five times as much carbon dioxide during the alkaline hydrolysis of proteins as during the acid hydrolysis indicates some type of acid-resistant urea grouping, such as is present in hydantoins. Two α-amino acids could be so linked as to form a "polypeptide hydantoin" that on alkaline hydrolysis would form only the α-amino acids and carbon dioxide. A number of such polypeptide hydantoins have been prepared by Johnson and his associates: for example, 5-*p*-hydroxybenzylhydantoin-1-acetic acid, which breaks down under alkaline hydrolysis to yield glycine, tyrosine, and carbon dioxide (372).



Further confirmation of Johnson's theory is to be found in the work of Wada, who reported that he had been able to isolate a hydantoin derivative from gelatin as a result of hydrolysis in aqueous-alcoholic hydrogen chloride (614). This same hydantoin, α-amino-ϵ-hydantoincaproic acid, also appeared to result from the hydrolysis of casein under similar conditions. While the hydantoins themselves were not isolated from a number of other proteins, the formation of urea from hydrolysates of these proteins, under conditions previously shown to cause hydantoin to break down to give urea, appears to indicate that hydantoin linkages may also be present in these proteins (615, 616).

II. METHODS OF SYNTHESIS OF HYDANTOINS

A. Amino acids and alkali cyanates or thiocyanates

One of the methods for the synthesis of hydantoins which has found wide application is that involving the reaction of α-amino acids with potassium cyanate.

This reaction, first introduced in 1873 by Urech (608), has been applied to the preparation of a large number of hydantoins with substituents in the *C*-5 position, as well as to a limited number of *N*-1 substituted hydantoins. When an α-amino acid reacts with potassium cyanate in aqueous solution, the product is generally the potassium salt of an α-ureido, or hydantoic, acid. The first product of the reaction may be assumed to be a substituted ammonium cyanate, which then undergoes the urea rearrangement to form the salt of the hydantoic acid.

$$\underset{\displaystyle NH_2}{\overset{\displaystyle CH_3CHCOOH}{|}} + KOCN \rightarrow \underset{\displaystyle NH_2\cdot HOCN}{\overset{\displaystyle CH_3CHCOOK}{|}} \rightarrow \underset{\displaystyle NHCONH_2}{\overset{\displaystyle CH_3CHCOOK}{|}}$$

The free hydantoic acids may often be precipitated from the aqueous solutions of their potassium salts by the addition of mineral acid. The most frequently used method for the conversion of hydantoic acids or their esters into the corresponding cyclic anhydrides, or hydantoins, was first described by Mouneyrat (468) and consists in heating with 25 per cent hydrochloric acid. Harries and Weiss obtained nearly quantitative yields of hydantoin from glycine ethyl ester hydrochloride through the use of this method (290).

$$\underset{\displaystyle HCl}{\overset{\displaystyle NH_2CH_2COOC_2H_5}{|}} \xrightarrow{KOCN} \begin{array}{l} H_2N \quad COOC_2H_5 \\ | \quad\quad | \\ OC \quad\quad | \\ | \quad\quad | \\ HN{-}CH_2 \end{array} \xrightarrow{HCl} \begin{array}{l} HN{-}CO \\ | \quad | \\ OC \quad | \\ | \quad | \\ HN{-}CH_2 \end{array}$$

The alpha carbon atom of the amino acid becomes the carbon in the *C*-5 position of the hydantoin ring, and any groups attached to it become *C*-5 substituents in the resulting hydantoin; similarly, an *N*-1 substituted hydantoin is obtained if the α-amino acid used in the synthesis has a substituent on the amino nitrogen. For example, alanine is converted into 5-methylhydantoin (608),

$$\underset{\displaystyle NH_2}{\overset{\displaystyle CH_3CHCOOH}{|}} \xrightarrow{KOCN;\ HCl} \begin{array}{l} HN{-}CO \\ | \quad | \\ OC \quad | \\ | \quad | \\ HN{-}CHCH_3 \end{array}$$

while sarcosine, or *N*-methylglycine, forms 1-methylhydantoin (43, 546).

$$CH_3NHCH_2COOH \xrightarrow{KOCN;\ HCl} \begin{array}{l} HN{-}CO \\ | \quad | \\ OC \quad | \\ | \quad | \\ CH_3N{-}CH_2 \end{array}$$

This general method of synthesis has been used with a large number of α-amino acids (see table 1), as well as with certain amides and nitriles. So generally applicable is this reaction of α-amino acids with potassium cyanate that Boyd has suggested its utilization as a method for separating the amino acids resulting from the hydrolysis of proteins (93). A system was developed for the separation of the simpler monoamino monocarboxylic acids, which are usually difficult to isolate because of their marked solubility in water. The corresponding hydantoin

derivatives are much less soluble in water, and can readily be separated by fractional crystallization. The α-amino acids may be regenerated through alkaline hydrolysis of the hydantoins; the chief disadvantage of this method is that racemic amino acids are obtained after the alkaline hydrolysis.

The procedure most frequently employed in the conversion of α-amino acids into their hydantoin derivatives is that developed by Dakin (168), in which the amino acids are boiled in concentrated aqueous solution with potassium cyanate,

TABLE 1

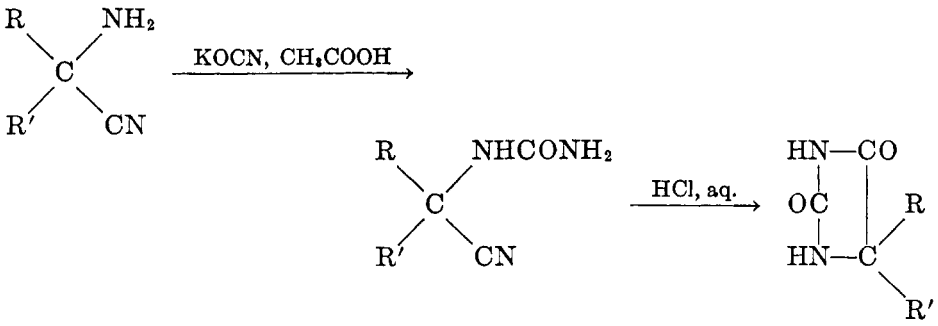
Amino acids and potassium cyanate

AMINO ACIDS	REFERENCES	AMINO ACIDS	REFERENCES
Alanine	(11, 93, 170, 291, 608, 626)	Histidine	(93)
		Hydrazinoacetic acid	(602)
α-Amino-*n*-butyric acid	(93)	Hydrazinodiisobutyric acid	(36)
α-Aminoisobutyric acid	(93, 607, 626)	Hydroxyproline	(93)
α-Amino-γ-hydroxybutyric acid	(436)	Leucine	(93, 168, 432)
α-Amino-α-phenylacetic acid	(409)	Isoleucine, norleucine	(93)
		Lysine	(93)
Arginine	(89)	Methionine	(93, 333)
Aspartic acid	(93, 168, 489, 626)	*N*-Methoxyglycine	(392)
		β-Phenylalanine	(93, 167, 173)
Cysteine	(93, 106, 396, 548)	β-Phenylalanine-*N*-acetic acid	(278, 284)
Cystine	(93, 99, 329)	*N*-Phenylglycine	(80, 153, 555)
3,5-Dibromotyrosine	(376)	Proline	(93)
β-(3,4-Dihydroxyphenyl)-alanine	(175)	Sarcosine	(43, 463, 546, 622)
α,β-Di(propylamino)propionic acid	(237)	Serine	(93)
		Tryptophan	(93)
Djenkolic acid	(17, 610)	Tyrosine	(93, 168, 169, 350, 626, 629)
N-Ethylalanine	(203)		
Glutamic acid	(93, 168, 171, 626)	Valine	(93)
Glycine	(11, 93, 290, 291, 466, 626, 634)	Isovaline	(93, 168)

excess mineral acid is added to the hot solution, and the hydantoins are precipitated when the solution is cooled. There have been a number of modifications of this general procedure, and the free amino acids are not always employed. The reaction has been carried on in ammonium sulfate solution (43); glacial acetic acid has also been used as a solvent (36). If the sulfate or hydrochloride of the amino acid is used, it is not necessary at the end of the reaction to add mineral acid in order to free the hydantoic acid; the use of ethyl or of butyl esters of the α-amino acids has also been recommended (290, 409, 466).

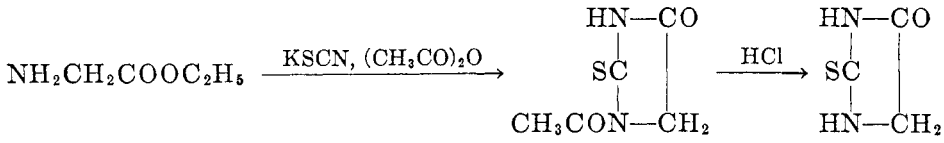
It has occasionally been found advantageous to use instead of the α-amino acids their amides (381) or their nitriles (33, 37, 80, 125, 152, 323, 398, 443, 518, 522,

598). A general method for the conversion of substituted α-amino nitriles into the corresponding *C*-5 substituted hydantoins was developed by Read (518); it was found that glacial acetic acid was a good solvent for the reaction of the nitrile with potassium cyanate, and that hydrolysis of the resulting α-ureido nitrile and ring closure to the corresponding hydantoin took place when the ureido compound was heated with mineral acid:



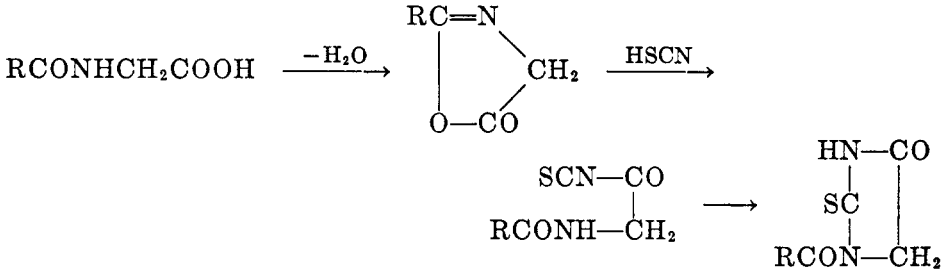
In this class of reactions may also be included the conversion of aldehyde ammonia into 5-methylhydantoin through the action of potassium cyanide, potassium cyanate, and hydrogen chloride (300, 609), since the primary reaction product is presumably an α-amino nitrile. Under similar conditions, acetone was converted into 5,5-dimethylhydantoin (605, 606, 607).

The reaction of potassium thiocyanate with α-amino acids might be expected to be analogous to that of potassium cyanate, but with the resultant formation of 2-thiohydantoins. It was reported by Klason (400), and later confirmed by Johnson (357), that 2-thiohydantoin is formed when the hydrochloride of glycine ethyl ester and potassium thiocyanate are heated together at 140–150°C. without solvent. Ethyl thiohydantoate was also isolated by Johnson from the reaction products, but the fact that he was unable, as were Harries and Weiss (290, 291), to bring about ring closure of this ester to 2-thiohydantoin indicates that ethyl thiohydantoate is not an intermediate product in the formation of 2-thiohydantoin. It was reported by Komatsu (407) that thiohydantoic acid had been obtained by heating glycine with potassium thiocyanate in acetic anhydride solution, and that 2-thiohydantoin could be prepared by heating this thiohydantoic acid with hydrochloric acid. Since it had been found impossible to bring about the cyclization of ethyl thiohydantoate with mineral acid, this reaction was investigated by Johnson and Nicolet (377), who concluded that Komatsu's "thiohydantoic acid" must have been 1-acetyl-2-thiohydantoin, which on heating with hydrochloric acid would be hydrolyzed to give acetic acid and 2-thiohydantoin.

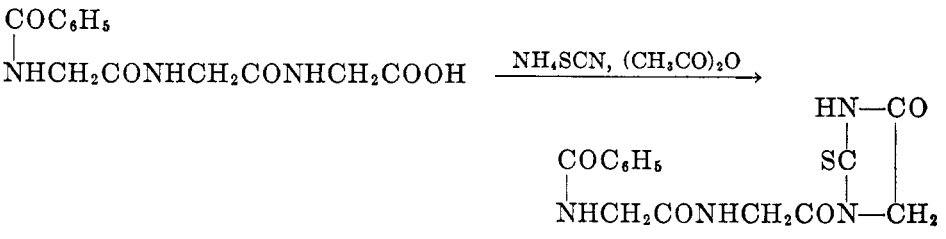


While several different reaction mechanisms have been suggested (355, 374, 377, 386, 408), the fact that a number of *N*-acyl α-amino acids have been found to undergo reaction with ammonium thiocyanate in acetic anhydride to form the corresponding 1-acyl-2-thiohydantoins (385), and also that 2-thiohydantoin is not acetylated by heating with acetic anhydride (377), make it reasonable to assume that acetylation of the α-amino acid precedes reaction with the potassium or ammonium thiocyanate.

It was soon discovered by Johnson that this reaction proceeds much more smoothly to give practically quantitative yields of the desired 2-thiohydantoins if ammonium thiocyanate is used in place of potassium thiocyanate (356, 380). Studies by Johnson and his associates (374, 386) indicate that this is not the result of thiourea formation, but that the very reactive isocyanic acid is formed more readily from ammonium thiocyanate than from any metallic salt of thiocyanic acid, and that it is this acid which combines with the *N*-acyl amino acid. The mechanism suggested by Johnson and Scott involves the intermediate formation first of a cyclic anhydride of the *N*-acyl amino acid and then of an acyl isothiocyanate; the latter then undergoes intramolecular rearrangement to form the 1-acyl-2-thiohydantoin (386):



This type of hydantoin synthesis, involving the reaction of ammonium thiocyanate in acetic anhydride solution, has been applied with success not only to a series of α-amino acids and their *N*-acyl derivatives (see table 2), but also to certain peptides (550). When a peptide is converted into a thiohydantoin derivative by this method, it is the terminal amino acid bearing a free carboxyl group which is attacked, and the rest of the peptide molecule is attached to the *N*-1 position of the thiohydantoin through an amide linkage.



Such a thiohydantoin derivative is readily hydrolyzed with dilute alkali to give a 2-thiohydantoin and a peptide containing one less amino acid than the original peptide. This procedure therefore affords a method for the systematic degradation

of polypeptides and for the determination of their constitution, since the amino acid which is removed in the form of its 2-thiohydantoin derivative can subsequently be identified through the properties of the 2-thiohydantoin.

B. Amino acids and alkyl or aryl isocyanates and isothiocyanates

Alkyl and aryl isocyanates and isothiocyanates, principally phenyl isocyanate and phenyl isothiocyanate, have found wide application in the synthesis of hydantoins and 2-thiohydantoins from α-amino acids (see table 3). Other isocyanates and isothiocyanates which have been used in the preparation of hydantoin derivatives include α-naphthyl isocyanate (45, 273, 454, 475, 476, 626), isohexyl isocyanate (165), *o*- and *m*-tolyl isothiocyanates (21, 32, 166, 454), methyl isothiocyanate (37, 181, 454), *p*-methoxyphenyl isothiocyanate (153), xylyl and

TABLE 2

Amino acids and potassium or ammonium thiocyanate

AMINO ACIDS	REFERENCES	AMINO ACIDS	REFERENCES
Alanine	(164, 346, 355, 380, 407)	Glutamic acid	(478)
		Glutathione	(480)
α-Aminoalanine, β-aminoalanine	(481)	Glycine	(290, 291, 356, 357, 377, 400, 407)
α-Amino-*n*-butyric acid	(346)		
α-Aminoisobutyric acid	(408)	Hippuric acid	(364, 380)
2-Aminoheptanoic acid	(346)	Leucine	(346, 408)
1-Aminohexahydrobenzoic acid	(113)	Isoleucine, norleucine	(346)
		Methionine	(346)
2-Aminoöctanoic acid	(346)	Phenylalanine	(346, 380)
α-Amino-α-phenylacetic acid	(153)	*N*-Phenylglycine	(408)
		Pyrrolidonecarboxylic acid	(369, 380)
α-Amino-*n*-valeric acid	(346)	Sarcosine	(408)
Asparagine	(370, 380)	Tyrosine	(380)
β-Cyclohexylalanine	(346)	Valine	(346, 408)
Cysteine, cystine	(479)		

allyl isothiocyanates (454), benzoyl isothiocyanate (191), tetraacetylglucose isothiocyanate (288), and isocyanate derivatives of anthracene, 1,2-benzanthrene (221), 3,4-benzopyrene (163), and *p*,*p*′-diaminodiphenyl sulfone (330). Since the use of these reagents leads to the formation of hydantoins carrying a substituent in the *N*-3 position, they are especially valuable when this type of hydantoin derivative is desired.

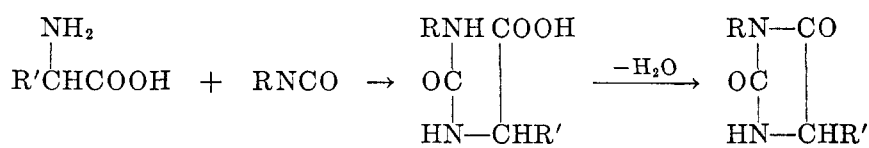
The reaction of the α-amino acid with the isocyanate is generally carried on in alkaline aqueous solution, from which the resulting ureido acid may usually be precipitated by the addition of mineral acid. In certain cases, however, it is the hydantoin, or cyclic anhydride of the ureido acid, which is obtained on acidifying the alkaline reaction mixture (98, 243, 619). The esters of the amino acids have also been used, ether being the solvent generally chosen for the reaction medium, and the corresponding esters of the ureido acids obtained (225). Both

the free hydantoic acids and their esters are readily converted into hydantoins, or into 2-thiohydantoins, by heating with mineral acid (409, 468).

TABLE 3

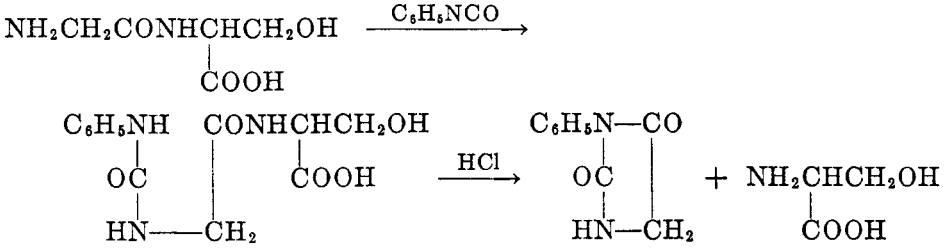
Amino acids and isocyanates and isothiocyanates

AMINO ACIDS	REFERENCES	AMINO ACIDS	REFERENCES
Alanine	(2, 20, 21, 273, 336, 390, 413, 454, 468 475, 490, 626)	Hydrazinoisobutyric acid	(31)
		Hydrazoisobutyric acid	(31)
		β-Hydroxyleucine, norleucine	(1)
		Iminodiacetic acid	(37)
		β-(*p*-Iodophenyl)alanine	(628)
α-Amino-*n*-butyric acid	(98, 468, 475)	Leucine	(20, 21, 224, 336, 468, 475)
α-Aminoisobutyric acid	(35, 454)		
1-Aminohexahydrobenzoic acid	(567)	Isoleucine, norleucine	(336, 476)
α-Amino-α-phenylacetic acid	(325, 409)	Lysine	(97, 172, 336, 397)
Derivatives	(293)	Methionine	(469, 570)
Asparagine	(98, 149, 476, 492)	*p*-Methoxyphenylalanine	(45)
		α-Methylaspartic acid	(151)
Aspartic acid	(98, 149, 336, 476, 492)	Ornithine	(172)
		β-Phenylalanine	(98, 229, 250, 456, 468, 476)
N-Benzylglycine	(601)		
β-Cyclohexylalanine	(563)		
Cysteine	(564)	β-Phenylalanine-*N*-acetic acid	(558)
Cystine	(98, 258, 336, 475, 494, 564)	*N*-Phenyl-β-phenylalanine	(389)
		β-Phenylserine	(47)
N,*N*′-Dimethylcystine	(86)	Proline	(98, 226)
N-Ethylglycine	(148)	Sarcosine	(243, 491)
α-Furyl-α-aminoacetic acid	(293)	Serine	(228, 419, 476, 583)
Glutamic acid	(98, 475)	Tryptophan	(476)
Glycine	(20, 21, 166, 225, 336, 454, 468, 475, 490, 626)	Tyrosine	(98, 336, 475, 492)
		Tyrosine-*N*-acetic acid	(619)
		Valine	(98, 476)
		Other aliphatic α-amino acids	(339, 340, 423)
Hexahydrotyrosine	(620)		
Hydrazinoacetic acid	(602)		



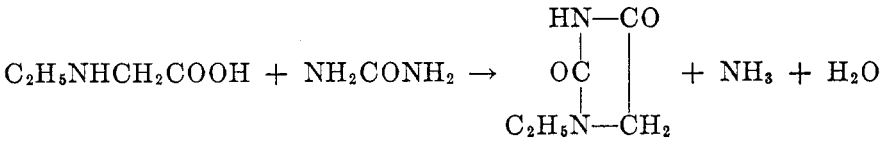
Amino nitriles react in a similar manner with isocyanates to form ureido derivatives; the latter may be converted into hydantoins by treatment with alcoholic hydrogen chloride (181).

This type of reaction has been utilized by M. Bergmann and his associates in their study of polypeptides (48, 49). Phenyl isocyanate will attack the terminal amino group of a peptide; for example, when glycylserine is treated with phenyl isocyanate in alkaline solution, and the reaction product heated with hydrochloric acid, *N*-3-phenylhydantoin and serine are obtained:



C. Amino acids and urea, or derivatives of urea

Urea and its derivatives have been used in a number of syntheses of hydantoins, most of these through the reaction of urea with α-amino acids (see table 4). Soon after the discovery of hydantoin, the first synthesis of this type was reported by Heintz, who found that when urea and *N*-ethylglycine were heated together at 120–125°C., ammonia was evolved and 1-ethylhydantoin formed (299):



This procedure of heating the reactants together without solvent was followed by a number of investigators for the preparation of hydantoins from glycine (263), sarcosine (43, 338, 342, 474, 555), and α-aminoisobutyric acid (298), as well as from other α-amino acids. *N*-Methylurea was reported to form 3-methylhydantoin when heated with glycine; *N*-phenylurea produced 3-phenylhydantoin (272).

It was found by Andreasch (11) that the yield of 5-methylhydantoin obtained by heating alanine with urea was about 15–20 per cent, whereas the synthesis of this same hydantoin from alanine and potassium cyanate gave nearly quantitative yields. It was then shown by Lippich (430, 431) that hydantoic acids, and through them hydantoins, could be obtained in better yield by boiling the amino acids in barium hydroxide solution with an excess of urea, a method first employed by Baumann and Hoppe-Seyler (43); the corresponding hydantoins were obtained by heating the barium salts of the hydantoic acids with dilute sulfuric acid. Lippich found that the reaction between urea and α-amino acids could also be carried on in aqueous solution, and that guanidine could be substituted for urea in this reaction (432).

Derivatives of urea can also be used in the synthesis of hydantoins from α-amino acids. Nitrourea can be used instead of urea (178), excellent yields of

hydantoin being obtained from nitrourea and glycine (544). Hydantoins have been prepared through the reaction of amino acids with esters of isothiourea (180) and with cyanamide (207, 209). It has also been found that when certain ureido acids, such as hydantoic acid or citrulline, are heated in aqueous solution, buffered to a pH of 7, with α-amino acids, the latter are partially converted into the corresponding hydantoic acids (420).

D. Urea and α-hydroxy acids, or α-hydroxy nitriles

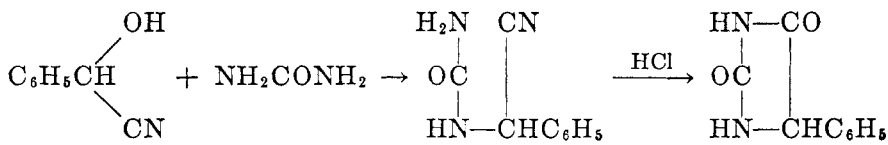
Not only α-amino acids, but also α-hydroxy acids and their nitriles, will react with urea to form hydantoic acids or hydantoins. Such reactions have been reported with benzilic acid (13), with 5-hydroxyhydantoin-5-carboxylic acid, which forms spiro-5,5-dihydantoin (65), and with cyanohydrins of the type

TABLE 4

Amino acids and urea

AMINO ACIDS	REFERENCES	AMINO ACIDS	REFERENCES
Alanine	(11, 431)	Histidine	(562)
α-Aminoisobutyric acid	(298, 431)	Leucine	(341, 430, 431, 432)
Asparagine	(265, 266, 267, 269, 270, 271)	Lysine	(337)
		N-Methylglycine	(474)
Aspartic acid	(269, 270, 271, 431, 432, 613)	β-Phenylalanine	(613)
		N-Phenylglycine	(555)
		Sarcosine	(43, 44, 338, 342, 555)
N-Ethylalanine	(203)		
N-Ethylglycine	(299, 474)	*N*-(*o*-Tolyl)glycine	(205)
Glutamic acid	(431, 613)	*N*-(*p*-Tolyl)glycine	(556)
Glycine	(43, 263, 272, 431, 432, 613)	Tyrosine	(431, 432, 613)
		Valine	(431)

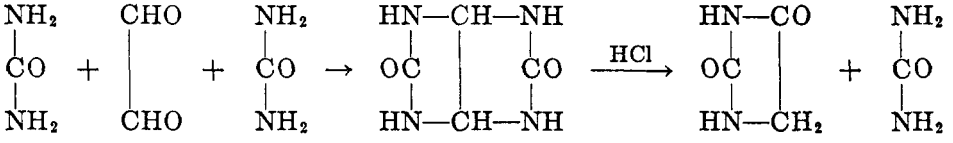
RCHOHCN, in which R is an aliphatic radical of at least four carbon atoms, a phenyl radical, or the radical $C_6H_5CH{=}CH{-}$ (509, 510, 511). The primary reaction product of urea with a cyanohydrin is an α-ureido nitrile; when this is heated with dilute mineral acid, hydrolysis of the nitrile group and ring closure to the hydantoin take place. In this way, 5-phenylhydantoin was prepared from benzaldehyde cyanohydrin (510):



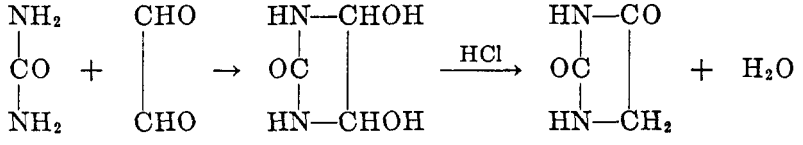
E. Urea and α-dicarbonyl compounds

It has been found that urea will react with compounds containing adjacent carbonyl groups, among them glyoxal, benzil, and α-keto acids, to form products which are readily converted into hydantoins. The first synthesis of this type was

reported by Siemonson (565), who obtained glycoluril as an intermediate product in the preparation of hydantoin from urea and glyoxal. When the glycoluril is heated with dilute hydrochloric acid, urea is split off and hydantoin obtained in good yields.

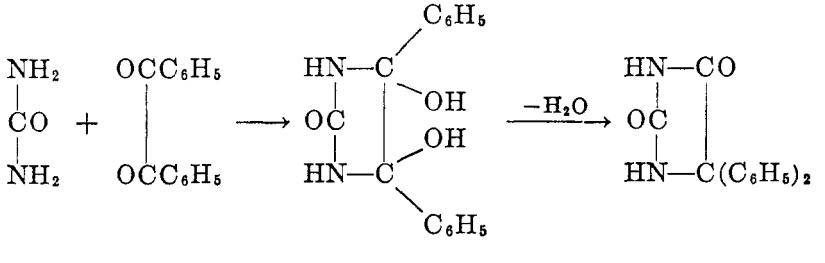


This reaction was studied further by Pauly and Sauter (495), who reported that they had been able to obtain a dihydroxy compound as an intermediate product; when the latter was heated with acid, a pinacolone rearrangement took place and hydantoin was formed:



The formation of this same intermediate product was postulated by Anschütz (16) in the synthesis of hydantoin from sodium dihydroxytartrate and urea; when these substances were heated in dilute hydrochloric acid, carbon dioxide was evolved and hydantoin formed.

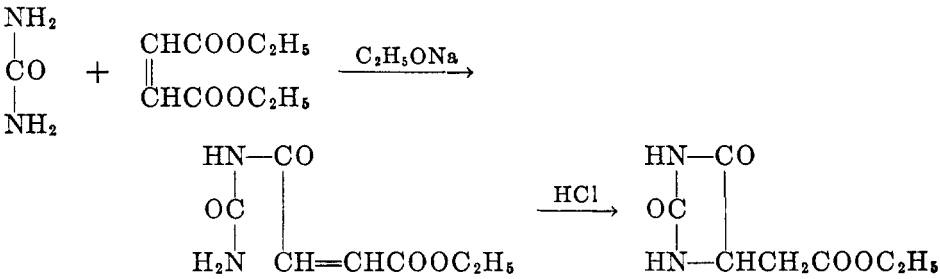
If methylurea is used in place of urea, two isomeric dimethylglycolurils are obtained, both of which break down on treatment with hydrochloric acid to give a mixture of *N*-1- and *N*-3-methylhydantoins (622). Methylglyoxal (559, 566) and phenylglyoxal (231) react similarly to glyoxal; the latter has been found useful in the synthesis of a series of 5-phenylhydantoins. The reaction of benzil with urea was studied extensively by Biltz, who recommended this method for the preparation of 5,5-diarylhydantoins (51, 52, 53, 54). The reaction can be carried on with *N*-substituted ureas, or with thioureas, leading to the formation of *N*-3 or of *N*-1, *N*-3 substituted hydantoins. Other diaryl α-diketones have been used (54, 259, 294, 429), or the benzil may be replaced with benzoin and an oxidizing agent such as an alkali hypohalite (108, 493). The fact that the same hydantoin, 1,3-dimethyl-5, 5-diphenylhydantoin, was obtained through the action of *N*,*N*′-dimethylurea with benzilic acid and with benzil (13, 53) shows that a pinacolone rearrangement must take place when the latter reacts with urea; the following mechanism for the reaction was suggested by Biltz (53):



The reaction of α-keto acids with urea may also lead to the hydantoin structure (176, 459, 464), but has not been developed into a general preparative method.

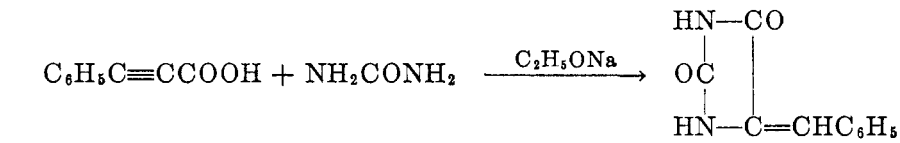
F. Urea and unsaturated acids

Certain unsaturated acids, both ethylenic and acetylenic, have been found to react with urea to produce hydantoins. In the presence of sodium ethoxide in alcoholic solution, urea will react with ethyl fumarate or with ethyl maleate to form a ureide; the latter when treated with dilute hydrochloric acid gives a mixture of ethyl hydantoin-5-acetate and its carbamido derivative (352).



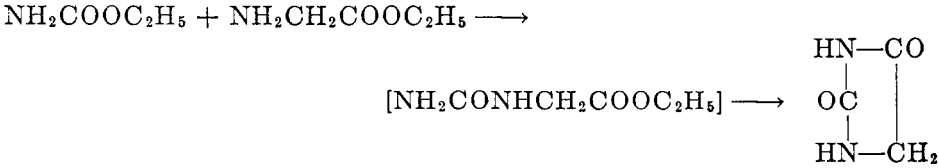
It should be noted, however, that the reaction of fumaric or of maleic acid with thiourea leads to the formation, not of a 2-thiohydantoin, but of a pseudothiohydantoin (10); furthermore, the reaction of ethyl cinnamate with urea produces, instead of the expected 5-benzylhydantoin, 4-phenyldihydrouracil (353). Tetracarbethoxyethene has been found to react with urea to produce spiro-5,5-dihydantoin (354).

An acetylenic acid, phenylpropiolic acid, was found to react in the form of its ester with urea in the presence of sodium ethoxide to form 5-benzalhydantoin (538, 539); the use of thiourea was reported to lead to the formation of 2-thio-5-benzalhydantoin.



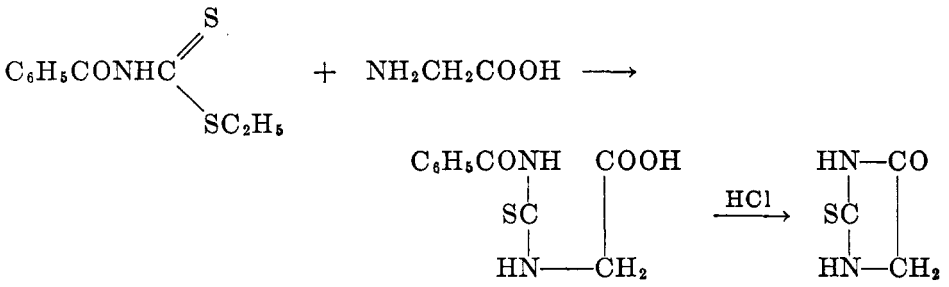
G. Amino acids and urethans

While hydantoic acids and hydantoins are usually prepared from α-amino acids through the action of cyanates, isocyanates, or urea, there have been a few isolated examples of other methods of preparation. It was discovered by Diels and Heintzel (189) that the sodium derivative of urethan would react with the ethyl ester of glycine in ether, hydantoin being isolated after evaporating the ether solution and acidifying the residue with hydrochloric acid.



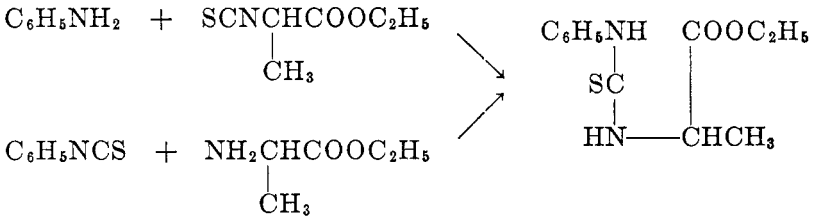
Isoamylurethan was used by Lippich in the preparation of a hydantoic acid from leucine; the amino acid was treated with a large excess of the urethan in boiling barium hydroxide solution (432).

It was shown by Wheeler, Nicolet, and Johnson (631) that dithiourethans would react in a similar manner with α-amino acids. For example, from ethyl *N*-benzoyldithiocarbamate and glycine was prepared benzoylthiohydantoic acid, which on heating with hydrochloric acid was converted into benzoic acid and 2-thiohydantoin.

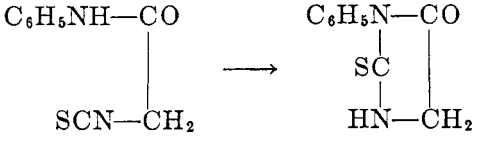


H. Isocyanates and isothiocyanates derived from amino acids, and amines

Certain isocyanates and isothiocyanates derived from α-amino acids, through the action of phosgene or of thiophosgene, have been utilized in the synthesis of hydantoins. These compounds will react with ammonia (341), amines (373, 390), or α-amino acids (384, 465) to give carbamido acids which may in turn be converted into hydantoins. For example, ethyl α-isothiocyanopropionate, prepared through the action of thiophosgene on alanine, gives with aniline the same phenylthiohydantoic ester which is obtained by treating the ethyl ester of alanine with phenyl isothiocyanate (390).

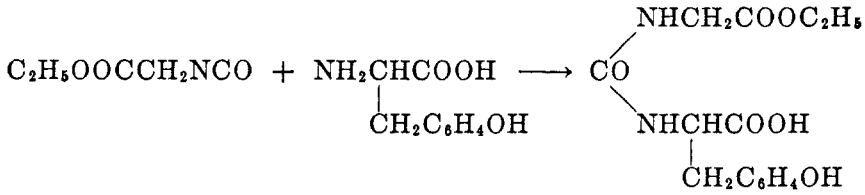


The reaction of ammonia with ethyl isothiocyanoacetate to form 2-thiohydantoin (373) has been shown to involve the intermediate formation of the amide of isothiocyanoacetic acid instead of ethyl thiohydantoate (375). Proof of this mechanism comes from the facts that ethyl thiohydantoate does not undergo cyclization to form 2-thiohydantoin (290), and that the anilide of isothiocyanoacetic acid undergoes spontaneous ring closure to form 2-thio-3-phenylhydantoin.

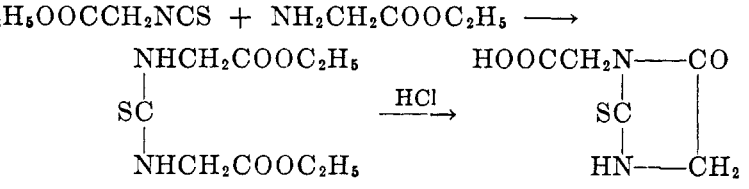


Other substituted isothiocyanoacetanilides have been prepared, and shown to react in the same manner (332). It should be noted that the normal thiocyanoacetic ester reacts with ammonia to form pseudothiohydantoin (375), and that thiocyanoacetanilide undergoes cyclization to form a substituted pseudothiohydantoin (332).

The reaction of isocyanoacetic esters with amino acids leads to the formation of another class of urea derivatives, the carbonylbisamino acids, or symmetrical carbamidodiacetic acids, which have been found to be of especial value in the preparation of 3-hydantoinacetic acids. The first compound of this type to be reported was prepared by Morel from ethyl isocyanoacetate and tyrosine (465).

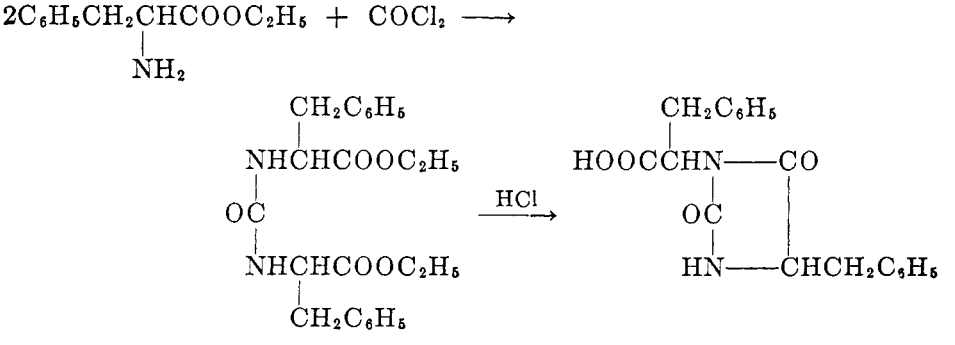


When heated with dilute mineral acid, these compounds undergo cyclization to form substituted hydantoins (260, 438, 624); for example, 2-thiohydantoin-3-acetic acid was prepared by Johnson and Renfrew by treating the intermediate reaction product of ethyl isothiocyanoacetate and glycine ethyl ester with dilute hydrochloric acid (384):



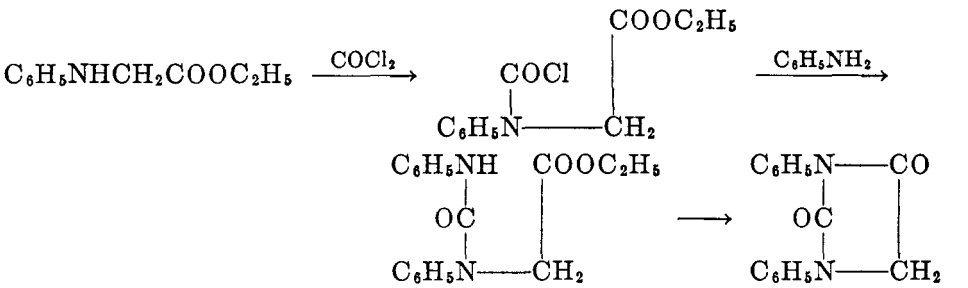
I. Amino acids and phosgene

The esters of symmetrical carbonylbisamino acids may also be prepared directly from amino acid esters under the action of phosgene (624); such esters have been prepared from the esters of glycine (415, 438, 624), alanine (261), phenylalanine (624), and aminomalonic acid (119, 438). From phenylalanine, for example, may be prepared carbonylbisphenylalanine and 5-benzylhydantoin-3-benzylacetic acid.

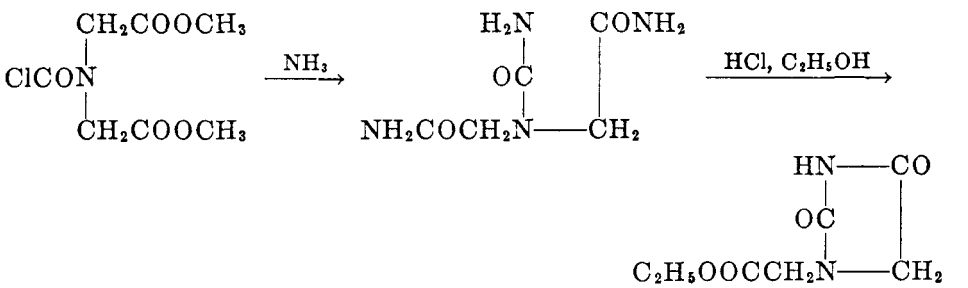


This method has been shown to be applicable to the preparation of 2-thiohydantoin-3-acetic acids (402, 403). The amino acid esters are allowed to react with carbon disulfide in the presence of sodium bicarbonate, instead of with phosgene, and the resulting disubstituted thioureas treated with alcoholic ammonia to bring about cyclization.

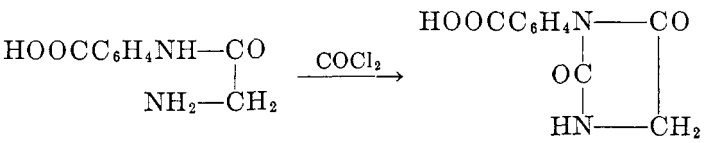
When the esters of certain *N*-substituted α-amino acids are treated with phosgene, an *N*-chloroformyl derivative is formed instead of a ureide. For example, the treatment of *N*-phenylglycine ester with phosgene produced an *N*-chloroformyl derivative, which with aniline gave a diphenyl derivative of ethyl hydantoate; this hydantoic ester was converted into 1,3-diphenylhydantoin when it was heated in boiling ethanol (301).



The reaction of phosgene with dimethyl iminodiacetate was found to produce either of two different products, depending on the experimental conditions; one of these was the *N*-chloroformyl derivative, the other dimethyl carbonyldiiminodiacetate (394). The *N*-chloroformyl derivative was readily converted into ethyl hydantoin-1-acetate through treatment first with alcoholic ammonia to form the diamide of ureidodiacetic acid, then with aqueous hydrochloric acid, and finally with alcoholic hydrogen chloride.

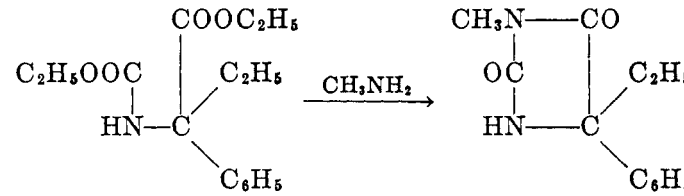


In the preparation of 3-*p*-carboxyphenylhydantoin from *N*-glycyl-*p*-aminobenzoic acid and phosgene, the hydantoin was obtained directly (603). While no intermediate products were isolated, the reaction presumably follows the course outlined above, involving the formation of an *N*-chloroformyl derivative prior to the establishment of the cyclic ureide structure.



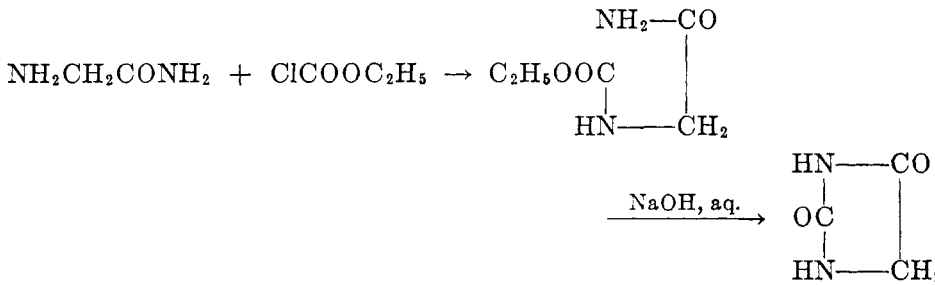
J. Amino acid esters and alkyl chloroformates

The treatment of esters of α-amino acids with ethyl chloroformate has been used to prepare *N*-carbethoxy derivatives of these amino acids. When the resulting urethanoacetic ester is treated with ammonia or with a primary amine, a substituted hydantoin is formed (126, 135, 138, 394). For example, the treatment of ethyl α-urethano-α-phenylbutyrate with methylamine in alcohol under pressure results in the formation of 3-methyl-5-phenyl-5-ethylhydantoin (135):

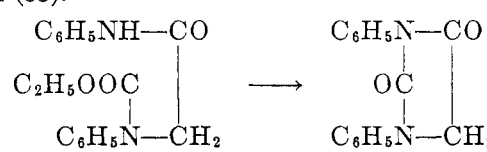


K. Amino acid amides and alkyl chloroformates

When the amide of an α-amino acid is treated with ethyl chloroformate to produce an *N*-carbethoxy derivative, subsequent treatment with ammonia is not necessary in order to form a hydantoin derivative. The method of synthesis of hydantoins from *N*-carbethoxyamino acid amides has been found to be of quite general application in the preparation of various substituted hydantoins. Cyclization of these compounds is brought about by dilute aqueous or alcoholic alkali (147, 404); the use of acid has been found to bring about hydrolysis of the amide instead of cyclization (230). By this method, Koenigs and Mylo prepared hydantoin from glycinamide (404),

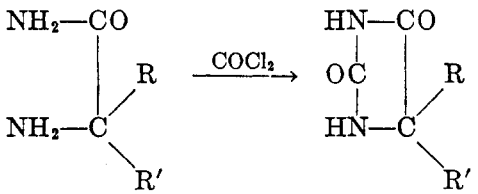


as well as 5-methylhydantoin from alanine, and 5-ethylhydantoin, 5-isobutylhydantoin, and 5-benzylhydantoin from the appropriate amino acids. Other hydantoins prepared by this general method include 5-phenylhydantoin (147, 418), 1-phenylhydantoin (444), 5-hydantoincarboxamide (381), 1-hydantoinacetic acid (394), and many others (132, 147, 209). Any substituents on the nitrogen of the amide group will appear in the *N*-3 position of the hydantoin; for example, the carbethoxy derivative of *N*-phenylglycine anilide will form 1,3-diphenylhydantoin (83).



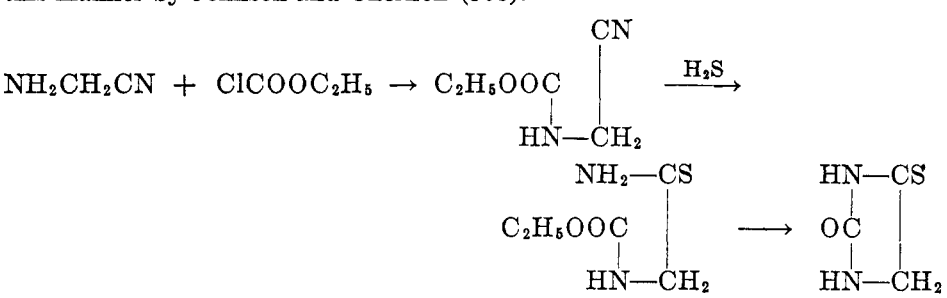
Other *N*-3-substituted hydantoins have been prepared in a similar manner (125, 332, 375).

A similar reaction, but leading directly to the hydantoin from an α-amino acid amide, involves the reaction of the amino acid amide with phosgene, oxalyl chloride, or diphenyl carbonate (125):



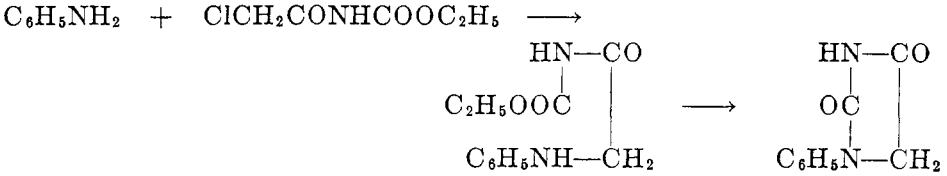
The use of carbon disulfide with an α-amino acid amide similarly leads to the formation of a 2-thiohydantoin (125).

The procedure in preparing the carbethoxyamino acid amides may be modified by treating an α-amino nitrile with ethyl chloroformate; the partial hydrolysis of the resulting carbethoxyamino nitrile results in the formation of the carbethoxyamino acid amide (418). Treatment of carbethoxyaminoacetonitrile with hydrogen sulfide leads to the formation of a thioamide, which undergoes cyclization to form 4-thiohydantoin; a number of 4-thiohydantoins were prepared in this manner by Johnson and Chernoff (368).

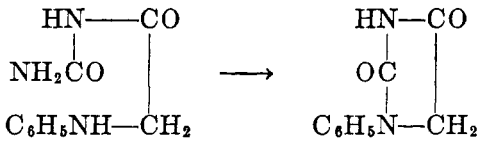


L. Chloroacetylurethan and amines

A method of preparation of hydantoins similar to that just discussed, but with ring closure between the *N*-1 and *C*-2 atoms instead of between the *C*-2 and *N*-3 atoms of the hydantoin ring, is the synthesis of 1-phenylhydantoin from chloroacetylurethan and aniline (238). It was shown that the aniline first reacted with the chloroacetylurethan to form *N*-phenylglycylurethan, which then could be transformed by heating into 1-phenylhydantoin.



Other aromatic amines could be substituted for aniline in this reaction. The corresponding amide, *N*-phenylglycylurea, was also converted by heat into 1-phenylhydantoin (238).

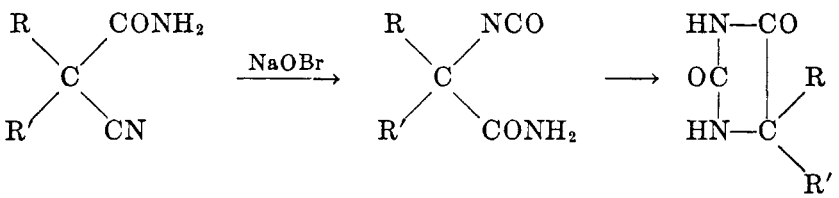


M. Bromoacetylurea

While Baeyer's synthesis of hydantoin from bromoacetylurea (27, 29) is of historical interest, it has proved to be of little practical importance, since difficulties are encountered in carrying on the reaction (470, 471) and the yields are at best very poor, as was shown by Biltz and Slotta after careful investigation of a number of possible experimental procedures (80). There have been several syntheses of substituted hydantoins utilizing this general method (3, 4, 22, 24, 174, 204, 240, 534), but the reported yields are invariably small. The conversion of certain substituted 5-bromobarbiturates into hydantoins by heating with alkali has been assumed to involve the intermediate formation and subsequent cyclization of derivatives of bromoacetylurea (23, 322).

N. Cyanoacetamides and alkali hypohalites

The synthesis of hydantoins through the action of alkali hypohalites on disubstituted cyanoacetamides has found wide application in the preparation of 5,5-disubstituted hydantoins (123, 127, 136, 139, 140, 141, 217, 218, 219, 220, 324, 326, 445, 573, 598). This reaction was first studied by Errera (213), who reported that this synthesis is not applicable to unsubstituted hydantoin. It is assumed that in the course of the reaction the amide group undergoes the Hofmann degradation to an isocyano group, which then immediately reacts with an amide group generated by the partial hydrolysis of the cyanide group.

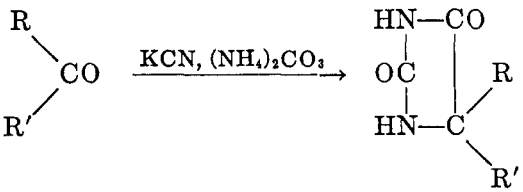


A substituted malonamide may be used in place of a cyanoacetamide (124, 343, 523); small yields of hydantoic acid were obtained from malonamide (621).

O. Bucherer–Bergs synthesis from carbonyl compounds

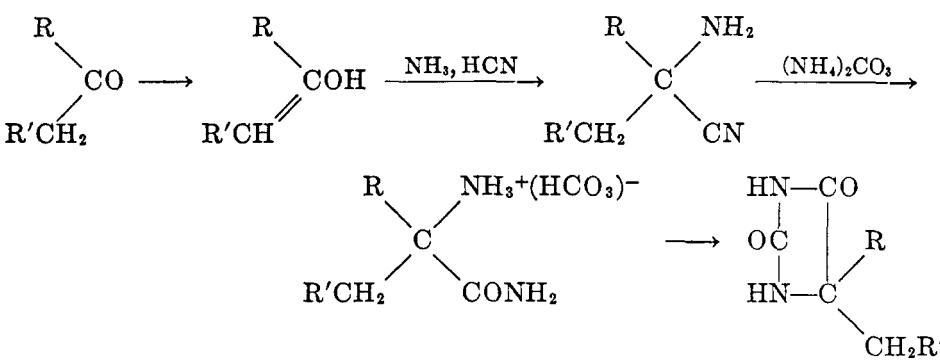
A method of synthesis of hydantoins which has assumed great prominence in recent years, particularly through the work of H. L. Henze and his associates, is the preparation of 5-substituted hydantoins from aldehydes and ketones through the action of potassium cyanide and ammonium carbonate. This method of synthesis has been found to be of quite general application to carbonyl compounds, and was made the basis of a system of identification of these compounds by Henze and Speer (318). The general procedure is to warm the carbonyl derivative

with 2 moles of potassium cyanide and 4 moles of ammonium carbonate in 50 per cent alcohol for 2 hr., after which the hydantoin may usually be isolated when the solution is cooled.



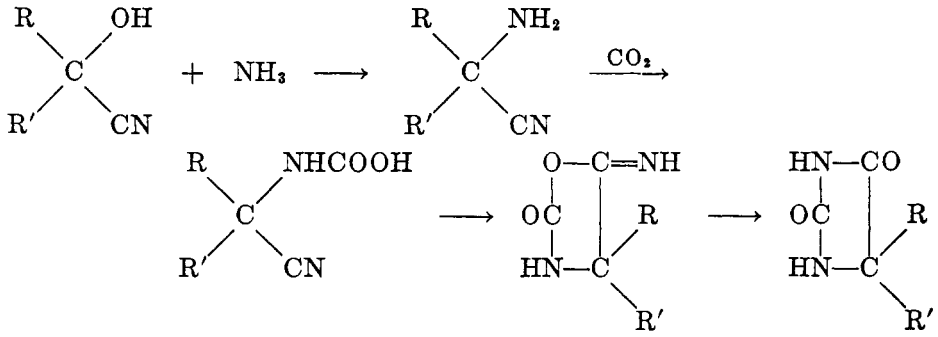
This method was found to be effective for many types of carbonyl compounds, with the exception of formaldehyde, certain unsaturated aldehydes, certain hydroxy- and nitro-aryl aldehydes, bisdimethylaminoacetone, and pyruvic acid.

Reactions of this type were first observed by Ciamician and Silber (145, 146), who obtained 5,5-dimethylhydantoin, together with a number of other substances, from a mixture of acetone and hydrocyanic acid which had been exposed to sunlight for a period of five to seven months, and by Bergs (50), who prepared a number of 5-substituted hydantoins from the corresponding aldehydes or ketones by treating them with potassium cyanide, ammonium carbonate, and carbon dioxide under several atmospheres of pressure at a temperature of 80°C. for 4–6 hr. The reaction was further studied by Slotta, Behnisch, and Szyszka (568), and the following mechanism for the reaction was suggested:



Bucherer and his associates, who obtained a hydantoin derivative as a by-product in the preparation of the cyanohydrin of cyclohexanone (101, 102, 103), found that the cyanohydrin reacted with ammonium carbonate to form a hydantoin, and that the reaction would take place at room temperature, or at a temperature not higher than 60–70°C., either in water solution or in benzene; the use of carbon dioxide under pressure, as recommended by Bergs, was not necessary. The mechanism of the reaction was studied by Bucherer and Steiner (105); it was found that cyanohydrins would react equally well to form hydantoins with ammonium carbonate or with ammonium carbamate, and that α-amino nitriles gave nearly quantitative yields of hydantoins when treated with carbon dioxide

in aqueous solution. The following mechanism was suggested:



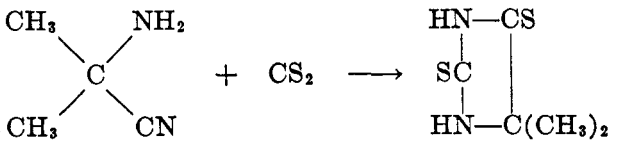
The procedure was further modified by Bucherer and Lieb (104, 424), who found that 50 per cent alcohol was an excellent solvent in which to carry on the reaction; under these conditions aldehydes, which had previously given poor results in this synthesis, reacted well, while ketones gave excellent yields of the hydantoins. Other solvents were also studied, and the optimum conditions for the reaction determined.

The original Bergs procedure was used by Pfeiffer and his associates in the synthesis of a large number of hydantoin derivatives as intermediates in the preparation of new α-amino acids (498, 499, 500, 501, 502, 503, 504). This procedure has also been followed in the syntheses of other hydantoins (129, 484, 569, 576, 577, 578), but has in general been replaced by the simpler method developed by Bucherer.

The Bucherer modification of the Bergs synthesis has been applied to a large number of carbonyl compounds of all types by Henze and his associates (5, 161, 162, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 318, 319, 321, 427, 446, 447, 451, 458, 522, 531, 532, 581, 585, 632). It was found that certain compounds, particularly certain amino ketones, which could not be converted into hydantoins by the Bergs method gave good results with the Bucherer modification (313, 451). The reaction of diaryl ketones was found to give the best results when fused acetamide was used as a solvent (310); a series of 5-(1-naphthyl)-5-substituted hydantoins was prepared by heating the corresponding ketones with potassium cyanide and ammonium carbonate in fused acetamide under pressure (315). Other solvents used by Henze included ethylene glycol, trimethylene glycol, ethanolamine, and dioxane (304).

This general method of hydantoin synthesis has been used by a number of other investigators in recent years (121, 122, 179, 251, 252, 253, 293, 440, 441, 442, 455, 485, 486, 488, 508, 513, 526, 533, 535, 584, 596, 597, 599). Hydrocyanic acid has been used in place of potassium cyanide, nearly quantitative yields of pure 5,5-dimethylhydantoin being obtained when acetone, hydrogen cyanide, and ammonium carbonate were warmed to 60–66°C. in aqueous solution (526). Although this reaction cannot be carried out with formaldehyde (318), unsubstituted hydantoin may be prepared if aminoacetonitrile is heated with ammonium carbonate in aqueous solution at 67–79°C. under pressure (262).

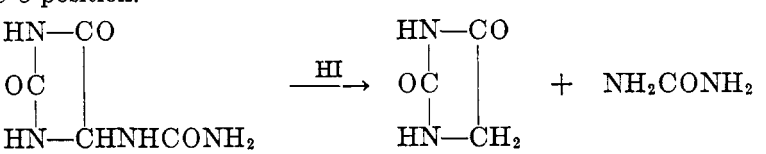
The reaction of α-amino nitriles with carbon disulfide instead of with carbon dioxide has been found to lead to the formation of 2,4-dithiohydantoins (111, 114, 157, 158, 159, 348, 349). For example, acetone cyanohydrin was converted into α-aminoisobutyronitrile, which reacted with carbon disulfide to form 2,4-dithio-5,5-dimethylhydantoin (349).



The ketones were used directly by Carrington (112) in a Bucherer-type reaction with carbon disulfide, ammonium chloride, and sodium cyanide, using methanol, ethanol, or benzene as solvent; nearly every ketone tested gave positive results, including some which do not react in the Bucherer synthesis using ammonium carbonate.

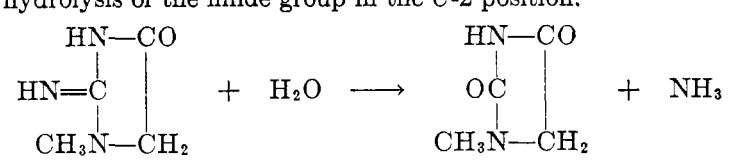
III. CONVERSION OF OTHER HETEROCYCLIC COMPOUNDS INTO HYDANTOINS

Hydantoins have been prepared from a number of other cyclic derivatives of urea, among them allantoin, creatinine, parabanic acid, purines, and pyrimidines. The discovery of hydantoin by Baeyer (25) was the result of a preparation of this type. Allantoin, itself a degradation product of uric acid, was treated with hydriodic acid, with the resultant cleavage of the urea group substituted in the *C*-5 position.



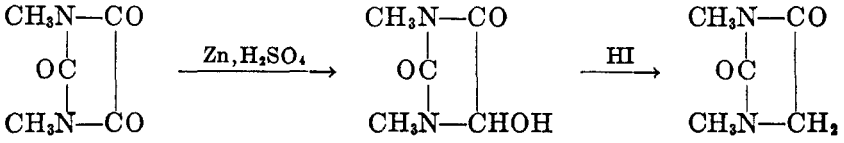
Reduction of allantoin with sodium amalgam was found to produce glycoluril (521); the latter was hydrolyzed by hot hydrochloric acid to form hydantoin (28) or by barium hydroxide to form hydantoic acid (521). Fischer and Ach prepared 1-methylhydantoin from the corresponding methylallantoin (227), while Biltz and his associates have prepared several other substituted hydantoins from allantoin derivatives (73, 74, 78).

Creatinine (474), as well as its 5-benzyl and 5-benzal derivatives (482), has been the source of 1-methylhydantoins. This method of preparation involves only the hydrolysis of the imide group in the *C*-2 position.

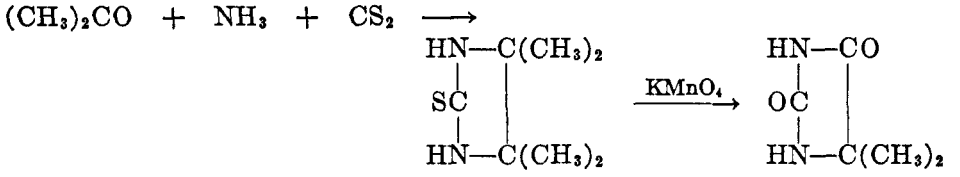


The reduction of parabanic acid, or of its *N*-methyl derivatives, has been shown to lead to the formation of hydantoins. The electrolytic reduction of parabanic acid leads directly to the formation of hydantoin (592), while studies by Andre-

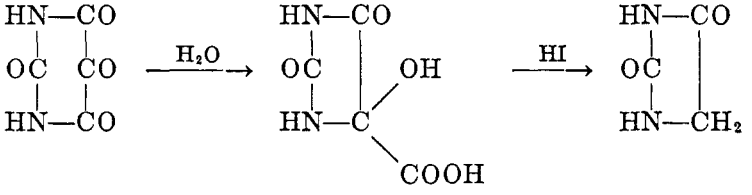
asch (8) and by Biltz and Heidrich (62) showed that the action of zinc and sulfuric acid on 1,3-dimethylparabanic acid produces 1,3-dimethyl-5-hydroxyhydantoin, which can then be reduced with hydriodic acid to 1,3-dimethylhydantoin; reduction with concentrated hydriodic acid produces only the dimethylhydantoin and not the intermediate hydroxy compound (63).



The oxidation of an imidazole derivative, obtained through the action of carbon disulfide and ammonia on acetone, was reported by Heilpern (298) to result in the formation of 5,5-dimethylhydantoin.

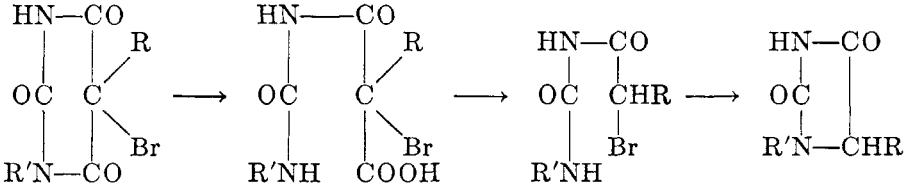


Soon after his discovery of hydantoin in 1861, Baeyer reported that he had obtained this same substance through the reduction of alloxanic acid (26), an acid obtained through the partial hydrolysis of alloxan. It was not until later, after the structures of the pyrimidines and hydantoins became known, that the mechanism of this reaction was understood. It was established in 1916 by Biltz, Heyn, and Bergius (65) that alloxanic acid is a hydantoin derivative, and that this method of preparation of hydantoin from alloxan involves the transformation of a pyrimidine into a hydantoin.



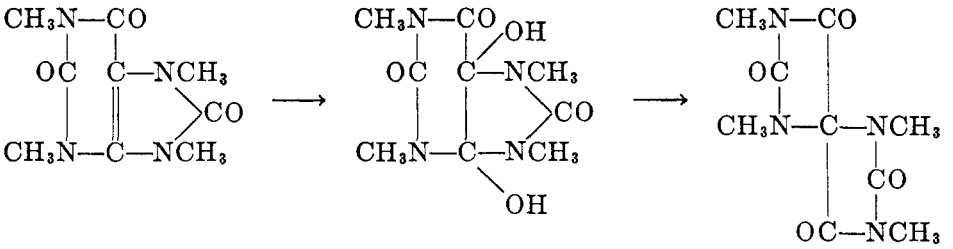
The oxidative degradation of alloxan 2-dimethylaminoanil was also found to lead to the formation of a hydantoin derivative (537).

Other pyrimidines have been converted into hydantoins, among them several 5-bromobarbituric acids (23, 322). The transformation of the latter, under the action of alkali, appears to involve the intermediate formation of a bromoacetylurea derivative, which then undergoes ring closure to form a hydantoin.



This reaction leads to the formation of two isomeric hydantoins when R′ is not hydrogen: the *N*-1 substituted hydantoin above, and an isomer in which the R′ is in the *N*-3 position. Also formed in this reaction is a 2-imino-4-oxazolidone; when alcoholic potassium hydroxide is used instead of aqueous alkali, the intermediate bromoacetylurea is almost completely converted into this product (23).

The degradation of purine derivatives, chiefly of uric acid and its substitution products, has been the source of a number of hydantoins. Various methods of degradation have been used, among them oxidation, reduction, and hydrolysis with acid or with alkali. Many unusual hydantoin derivatives, difficult to obtain by other methods of synthesis, have been prepared from purines. For example, tetramethylspiro-5,5-dihydantoin was prepared by the oxidation of tetramethyluric acid (66). Biltz suggested that a glycol was formed as an intermediate product, and that this glycol underwent a pinacolone rearrangement to give the spiro-5,5-dihydantoin.



Numerous other hydantoin derivatives have been prepared through uric acid degradations, to which individual reference will not be made (55, 56, 57, 58, 59, 61, 64, 67, 69, 70, 72, 74, 75, 76, 81, 82, 223, 248, 249, 264, 506). This work has been carried on by a number of different investigators, in recent years chiefly by H. Biltz and his associates. Studies on the oxidation of uric acid, with the *N*-1, *N*-3, and *N*-9 positions occupied by the N^{15} isotope, have recently been made; hydantoins have been obtained which appear to be formed from the ureide groups both in the five-membered and in the six-membered ring (117).

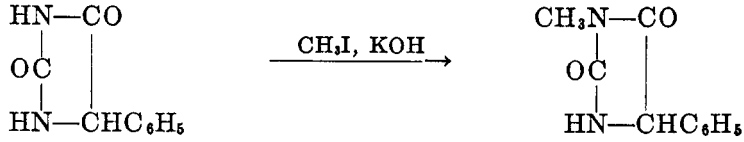
IV. INTRODUCTION OF SUBSTITUENTS INTO THE HYDANTOIN RING

A. Substitution in the N-1 and N-3 positions

While many *N*-substituted hydantoins have been prepared by synthesizing the hydantoins from compounds bearing the appropriate substituents attached to nitrogen atoms, it is also possible to introduce substituents onto these nitrogen atoms in the hydantoin ring. There are certain limitations, since hydantoins which are substituted in the *N*-1 position alone cannot normally be prepared by direct alkylation; *N*-3 aryl hydantoins are also obtained by other methods, chiefly through the interaction of aryl isocyanates and α-amino acids.

It was discovered by Pinner that hydantoins could be alkylated in the *N*-3 position by treatment with alkyl halides in alkaline solution (509). By heating 5-phenylhydantoin with methyl iodide in the presence of one equivalent of

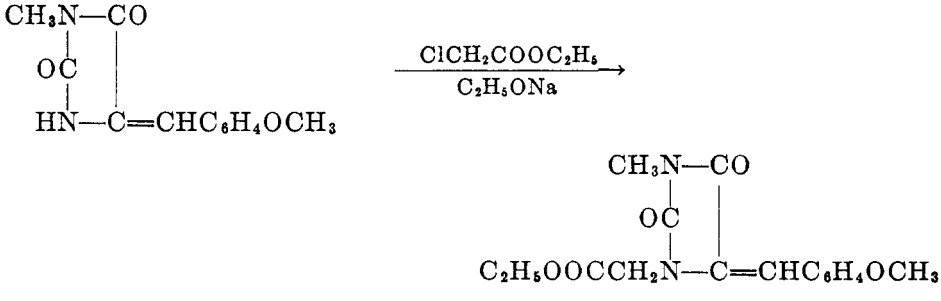
potassium hydroxide in methanol, 3-methyl-5-phenylhydantoin was prepared:



This same procedure was followed in the *N*-3 alkylation of hydantoin (291) and of 1-phenylhydantoin (239). The *N*-3 acetic acid derivative of 1-phenyl-5-methylhydantoin was prepared by treating this hydantoin with chloroacetic acid in alkaline alcoholic solution (240). Other alkylating agents which have been used include dimethyl sulfate (53, 130, 131, 134, 137, 142, 575), diazomethane (68), ethyl bromide in pyridine (133), and *p*-nitrobenzyl chloride (208, 428).

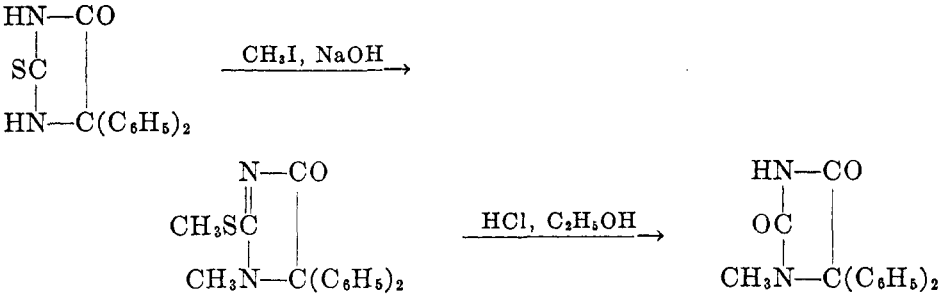
While *N*-3 alkylation of a hydantoin usually proceeds smoothly, *N*-1 substituents cannot be introduced, through action of alkyl halides in alkaline solution, into a hydantoin which does not have a double bond or a phenyl group attached to the *C*-5 carbon atom. For example, Siemonson tried unsuccessfully to introduce a second methyl group into 1-methylhydantoin (565). This was stated as a general rule by Johnson and Bates: "In the case of plain hydantoin, and related saturated methylene derivatives so far examined, the [3] position is the point of attack, and the formation of [1] and 1,3-alkyl derivatives has never been observed." (361) The greater reactivity of the *N*-3 position is presumably due to its favorable location between two activating carbonyl groups. The 1,3-dimethyl derivative of 5,5-diphenylhydantoin has been prepared, but through the action of dimethyl sulfate on the 1,3-dichloro derivative (60).

When the *C*-5 carbon atom of a hydantoin is attached to another atom by means of a double bond, the *N*-1 position is also activated and alkyl groups may readily be introduced into that position (378). The *N*-3 position is still the more active, as is shown by the alkylation of 5-anisalhydantoin: when one equivalent each of methyl iodide and of base was used, alkylation took place in the *N*-3 position only, but when two equivalents of methyl iodide and of base were added, 5-anisalhydantoin was converted into 1,3-dimethyl-5-anisalhydantoin. This activation of the *N*-1 position by *C*-5 unsaturation is also shown by the work of Pickett and McLean (507): *N*-3-methyl-5-benzalhydantoin was found to be acidic, while *N*-3-methyl-5-benzylhydantoin showed no acidic properties. Differ-



ent groups may be introduced into the *N*-1 position by treating an unsaturated hydantoin derivative of the type of 3-methyl-5-benzalhydantoin with various halogen derivatives; for example, ethyl 3-methyl-5-anisalhydantoin-1-acetate was prepared by Hahn and Renfrew through the reaction of the sodium derivative of 3-methyl-5-anisalhydantoin with ethyl chloroacetate in alcohol solution (286) (See page 428). A number of other unsaturated derivatives of 1-hydantoinacetic acid have been prepared in this way by D. A. Hahn and her associates (275, 280, 281, 435).

A method of obtaining *N*-1 alkyl derivatives of certain 5,5-disubstituted hydantoins has recently been reported by Cattelain and Chabrier (116). When 5,5-diphenyl-2-thiohydantoin was treated with methyl iodide in sodium hydroxide, it formed first an alkylmercapto derivative and then reacted with a second molecule of methyl iodide; when this dimethyl derivative of 5,5-diphenyl-2-thiohydantoin was treated with alcoholic hydrogen chloride, methyl mercaptan was split off and *N*-1-methyl-5,5-diphenylhydantoin obtained.

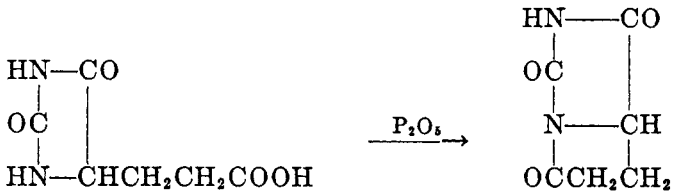


The product was shown to be isomeric with 3-methyl-5,5-diphenylhydantoin obtained by other methods. Similar results were obtained with other 5,5-disubstituted 2-thiohydantoins.

When hydantoins are treated with such reagents as acetic anhydride, sodium hypochlorite, or nitric acid, substitution appears to take place more readily on the nitrogen atom in the *N*-1 position, followed by the formation of a 1,3-disubstituted hydantoin.

Acetyl derivatives of hydantoins have been prepared by treating the hydantoins with acetic anhydride (128, 291, 509). The 1,3-diacetyl derivative of hydantoin was reported by Siemonson (565); it was found that this compound was readily hydrolyzed to form 1-acetylhydantoin. Only a monoacetyl derivative could be obtained from 3-methylhydantoin. Two isomeric acetyl derivatives of 5,5-dimethylhydantoin have been distinguished by Salmon and Kozlowski (547): the 1-acetyl derivative previously prepared by Biltz and Slotta (80), which is soluble in dilute alkali, and either the 3-acetyl or more probably the 2-enol acetate derivative which has been reported by Bucherer and Steiner (105) and which is hydrolyzed very readily. The dehydration of 5-hydantoinpropionic acid was found to lead to the formation of hydantoin-5-propio-1-lactam, a cyclic an-

hydride involving acylation of the nitrogen in the *N*-1 position (590):

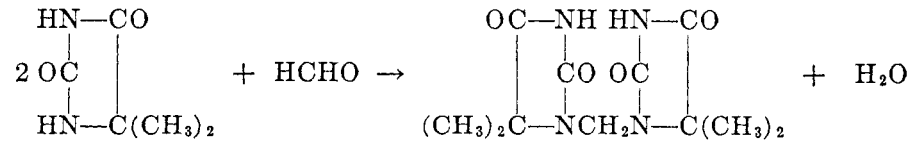


The corresponding derivative of 2-thiohydantoin had been obtained by Johnson and Guest (369) through the action of ammonium thiocyanate on pyrrolidonecarboxylic acid.

The action of nitric acid on hydantoins was studied by Franchimont and his associates (233, 234, 235, 236). Their conclusion that nitration takes place in the *N*-1 position was based on the fact that mononitro derivatives could be obtained from 3-methylhydantoin as well as from hydantoin, 5-methylhydantoin, and 5,5-dimethylhydantoin. This structure is in accord with the work of Stuckey (589) on the absorption spectra of nitrohydantoin in acid and in alkaline solution, since these studies indicate the presence of a labile hydrogen atom in the *N*-3 position.

The reaction of chlorine with hydantoin was first studied by Harries and Weiss (291); a dichloro derivative was obtained, from which the chlorine was removed to give hydantoin again when it was treated with ammonia. Biltz and Behrens (60) found that hypochlorous acid and sodium hypochlorite would both act to chlorinate 5,5-disubstituted hydantoins, but that sodium hypochlorite gave the *N*-3 sodium derivative of an *N*-1-chlorohydantoin, which on acidification gave the 1-chlorohydantoin, while hypochlorous acid in excess gave 1,3-dichlorohydantoins. Another chlorinating agent which will form 1,3-dichlorohydantoins is methyl *N*,*N*-dichlorocarbamate (91, 120). The formation of a dichloro derivative of 5,5-diphenylhydantoin has been utilized in a quantitative determination of that substance (412), while a number of chlorinated hydantoins have been patented as useful bleaching agents, antiseptics, and germicides (497, 527, 528, 529, 530).

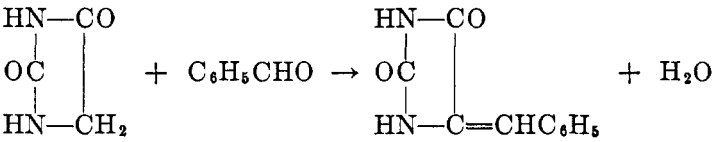
The reaction of formaldehyde with hydantoin does not follow the usual course of *C*-5 condensation observed with aromatic aldehydes, but involves substitution in the *N*-1 position. This reaction was first studied by Behrend and Niemeyer (46), who obtained a product which they were unable to identify, although it appeared to be 1-hydroxymethylhydantoin. It has been shown recently that when 5,5-disubstituted hydantoins are treated with formaldehyde in the presence of concentrated hydrochloric acid, 1,1′-methylenedihydantoins are formed (530, 617, 618).



B. Substitution in the C-5 position

While many *C*-5 substituted hydantoins have been prepared by using appropriately substituted compounds in the various syntheses which lead to the formation of hydantoins, it has often been found more convenient to prepare substitution products of this type through the condensation of hydantoin, or of hydantoins having a free methylene group in the *C*-5 position, with aromatic aldehydes or with other compounds which are reactive toward activated methylene groups.

It was first shown by Wheeler and Hoffman (629) that hydantoin will condense with aromatic aldehydes to give *C*-5 unsaturated hydantoin derivatives. The reaction was carried on in glacial acetic acid to which had been added fused sodium acetate and acetic anhydride, and was found to proceed smoothly with a number of aromatic aldehydes. For example, hydantoin was condensed with benzaldehyde to give 5-benzalhydantoin:



It has been found that 2-thiohydantoins also undergo condensations of this type, and that they frequently condense more readily than the corresponding oxygen hydantoins (387, 627).

While most of the condensations of hydantoins with aldehydes have been carried on in the glacial acetic acid medium recommended by Wheeler and Hoffman, it was observed by Boyd and Robson (94) that condensation would also take place in pyridine to which had been added either piperidine or diethylamine as condensing agents at a temperature of 100–120°C. Of these two agents, diethylamine was much more effective, since in the condensation between hydantoin and anisaldehyde, piperidine gave a 14 per cent yield, while a 94 per cent yield was obtained when diethylamine was used. However, when 1-acetyl-2-thiohydantoin was tested under similar conditions, the yields of condensation products were practically quantitative even when piperidine was the condensing agent employed. Piperidine alone has also been used as the condensation medium (292, 463); other condensing agents include dimethylaniline, morpholine (582), and di- or tri-alkanolamines (437). When aldehydes derived from quinoline were allowed to react with hydantoin in alcohol solution to which had been added a small amount of diethylamine, the intermediate aldol products were isolated; these were converted into the normal type of unsaturated condensation product by treatment with aqueous hydrochloric acid (505).

The method developed by Wheeler and Hoffman has been applied to the synthesis of a large number of 5-substituted hydantoins and 2-thiohydantoins (see table 5). Condensation reactions have been observed not only with various substituted benzaldehydes, but also with certain other aldehydes as well as

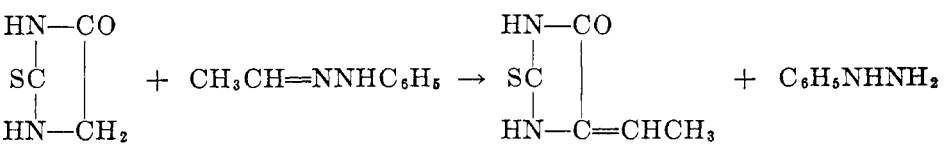
with a few other compounds of different types. Nicolet observed that aldehyde diacetates and phenylhydrazones would react with 2-thiohydantoin (477); by using the phenylhydrazone of acetaldehyde, he was able to prepare an aliphatic

TABLE 5

Carbonyl compounds condensed with hydantoins

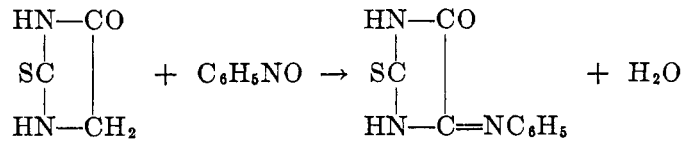
CARBONYL COMPOUNDS	REFERENCES	CARBONYL COMPOUNDS	REFERENCES
Aminobenzaldehyde (2-, 3-, or 4-amino)	(472)	2-Hydroxybenzaldehyde	(387, 472, 519, 627, 629)
Anisaldehyde	(94, 260, 382, 472, 519, 520, 627, 629, 637)	3-Hydroxybenzaldehyde	(472)
		4-Hydroxybenzaldehyde	(94, 472, 637)
		5-(Hydroxymethyl)furfural	(344)
		2-Hydroxy-4-nitrobenzaldehyde	(388)
Benzaldehyde	(63, 94, 260, 361, 371, 382, 472, 482, 520, 627, 629, 637)	3-Indolealdehyde	(96, 206, 437, 452, 561)
		3-Indolealdehyde derivatives	(257, 292, 524, 582)
3-Bromo-4-methoxybenzaldehyde	(363)	Isatin	(331, 410)
		Isatin derivatives	(331, 636)
2-Chlorobenzaldehyde	(320)	4-Methyl-4'-aldehydediphenyl sulfide	(417)
Cinchoninaldehyde	(505)		
Cinnamaldehyde	(391, 472, 627)	1-Methylimidazole-5-aldehyde	(545)
Cyclohexanone	(196)	Nicotinaldehyde	(483)
3,5-Dibromo-4-hydroxybenzaldehyde	(376)	2-Nitrobenzaldehyde	(411, 472)
		3-Nitrobenzaldehyde	(320, 472)
3,5-Dichloro-4-hydroxybenzaldehyde	(629)	4-Nitrobenzaldehyde	(472, 627, 629)
		3-Oxindolealdehyde	(345)
2,4-Dihydroxybenzaldehyde	(334, 472)	Parabanic acid	(71)
3,4-Dihydroxybenzaldehyde derivatives	(185, 186)	Piperonal	(184, 382, 472, 519, 627, 629)
2,4-Dimethoxybenzaldehyde	(183)	2-Pyrrolealdehyde	(327)
		Quinaldehyde	(505)
3,4-Dimethoxybenzaldehyde	(365)	2-Thiophenealdehyde	(39, 202)
		Trimethoxybenzaldehyde	
4-(Dimethylamino)benzaldehyde	(194, 472)	(2,3,4- and 3,4,5-)	(549)
		(2,4,5-)	(351, 591)
Enanthal (heptaldehyde)	(359)	Vanillin	(365, 472)
Furfural	(182, 202, 627, 629)		

hydantoin derivative corresponding to those obtained by using aromatic aldehydes.



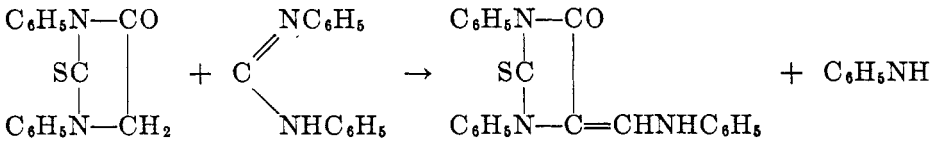
While substituted aliphatic aldehydes such as phenylacetaldehyde (391) and *p*-methoxyphenylacetaldehyde (214) will not condense with hydantoins, it was found by Johnson (359) that enanthal (or heptaldehyde) could be condensed with hydantoin; this was the first reported condensation of an aliphatic aldehyde with a hydantoin. Successful condensations have been carried on with α,β-unsaturated aldehydes,—for example, with cinnamaldehyde (391) and with α-hydroxymethylenephenylacetaldehyde (540). Aldehydes derived from a number of different heterocyclic compounds have been found to react with hydantoins in the same manner as does benzaldehyde, among them aldehyde derivatives of furan, thiophene, pyrrole, pyridine, quinoline, indole, and imidazole; several cyclic ketones have also been condensed with hydantoins, including isatin, parabanic acid, and cyclohexanone (see table 5).

The condensation of 2-thiohydantoin with a number of aromatic nitroso and isonitroso compounds was studied by Pendse and Dutt (496). The products were intensely colored compounds which were soluble in dilute alkali. For example, 2-thiohydantoin was heated in acetic anhydride solution with nitrosobenzene, and the condensation product obtained as a dark brown solid:



Compounds of this type were found by Dubsky (194, 196) to be useful as qualitative reagents for silver, mercury, and copper ions.

Substituted formamidines of the type RNHCH=NR′ have also been found to react with hydantoins (166); the reaction of diphenylformamidine with 1,3-diphenyl-2-thiohydantoin proceeds in the following manner:



While hydantoin and *N*-3 substituted hydantoins will condense readily with aromatic aldehydes, difficulty is often encountered in the preparation of aldehyde condensation products of *N*-1 substituted hydantoins. Wheeler and Hoffman were unable to condense either 1-phenylhydantoin or 1,3-diphenylhydantoin with anisaldehyde, while 3-phenylhydantoin condensed readily (629). Benzaldehyde, on the other hand, was found to react with 1,3-diphenylhydantoin (371). Other *N*-1 substituted hydantoins which either would not react with benzaldehyde or gave small yields of the benzal derivatives included 1,3-dimethylhydantoin (63), 1-methylhydantoin (482), and ethyl 1-hydantoinacetate (361). Condensations of 1-methylhydantoin with 3-indolealdehyde (463) and with 5-methylindole-3-aldehyde (257) have been reported; the dianilide of creatininephosphoric acid, a derivative of 1-methylhydantoin, would not condense with benzaldehyde, but would react with 4-hydroxybenzaldehyde and with 4-methoxybenzaldehyde (637).

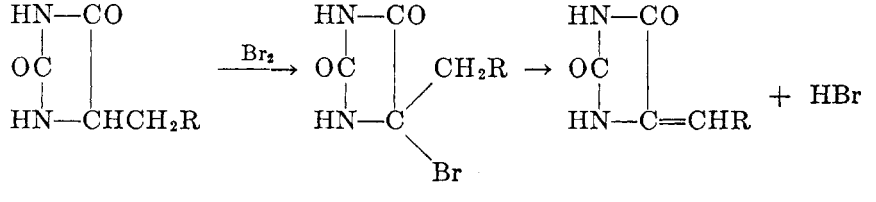
It was discovered by Wheeler and Brautlecht (627) that 2-thiohydantoins condense more readily with aromatic aldehydes than do the corresponding oxygen hydantoins. Not only does 2-thio-3-phenylhydantoin condense more readily than 3-phenylhydantoin, but condensation products may also be obtained with *N*-1 substituted 2-thiohydantoins such as 1-phenyl-2-thiohydantoin and 1,3-diphenyl-2-thiohydantoin. A similar difference in behavior between 3-hydantoinacetic acid and 2-thiohydantoin-3-acetic acid was noted by Renfrew and Johnson (519), since the latter compound reacted much more satisfactorily with a series of aromatic aldehydes.

The *C*-5 unsaturated hydantoin derivatives obtained as a result of condensation reactions may be reduced by any of a number of common reducing agents. Among those most frequently used are hydrogen iodide and red phosphorus (629), sodium amalgam (362, 367), and ammonium sulfide (95); other reagents include aluminum amalgam (629), hydrogen iodide in glacial acetic acid (630), tin and hydrochloric acid (367), tin and hydrogen chloride in ethanol (378), and hydrogen sulfide dissolved in pyridine, or in aqueous solutions of sodium or barium sulfide (95). Catalytic reductions have also been carried on, using palladium in alcohol (281) or Raney nickel in sodium hydroxide (206).

Cleavage of the hydantoin ring accompanies the use of some of these reagents. Sodium amalgam produces the sodium salts of the hydantoic acids, while still further hydrolysis to α-amino acids has been found to occur after long heating with hydrogen iodide and red phosphorus (629) or with aqueous ammonium sulfide (95). Tin and hydrochloric acid not only reduced the ethylenic double bond of 2-thio-5-benzalhydantoin, but also hydrolyzed the hydantoin to form β-phenylalanine (382).

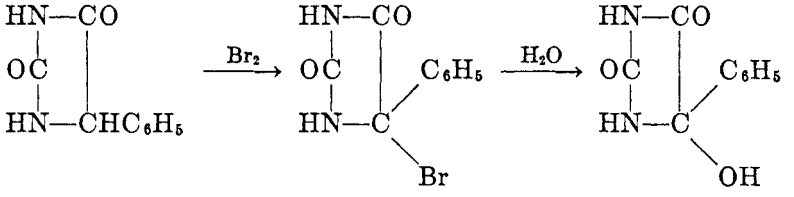
Some hydantoin derivatives are much more difficult to reduce than others, and one reagent will be effective where another will not. For example, 5-anisalhydantoin cannot be reduced with tin and aqueous hydrogen chloride or with zinc and acetic acid (630), but the reduction has been successfully carried out with tin and alcoholic hydrogen chloride (378), with hydrogen iodide in glacial acetic acid (630), and with sodium amalgam in alkaline aqueous solution (362). Johnson and Brautlecht found that the aldehyde condensation products of 3-phenyl-2-thiohydantoin were more difficult to reduce than the corresponding derivatives of 3-phenylhydantoin (366).

The action of bromine on hydantoins which have an unsubstituted hydrogen atom in the *C*-5 position is to replace that hydrogen atom. If there is a group attached to the *C*-5 position whose structure makes such a reaction possible, the compound then loses one molecule of hydrogen bromide to form a *C*-5 unsaturated hydantoin derivative (11, 244).

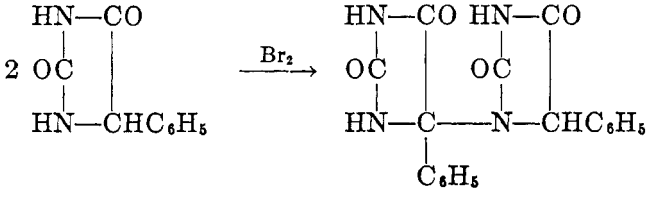


Such behavior, with resultant formation of unsaturated hydantoins, has been observed with *p*-hydroxybenzylhydantoin (376), 5-hydantoinacetic acid (489), and 5-hydantoinpropionic acid (171), although it was reported that a 5-bromo substitution product of 1-phenyl-3-methyl-5-iospropylhydantoin could be isolated (322).

It was found by Gabriel (245) that when 5-phenylhydantoin was treated with bromine in acetic acid, 5-bromo-5-phenylhydantoin was obtained; hydrolysis of this 5-bromohydantoin with hot water led to the formation of 5-hydroxy-5-phenylhydantoin.

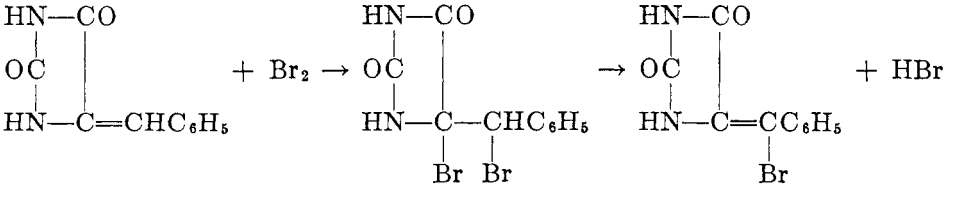


The bromine could also be replaced by an amino group through the action of alcoholic ammonia, or by a phenylamino group when the bromohydantoin was treated with aniline. When half an equivalent of bromine was used with 5-phenylhydantoin, the product obtained consisted of two hydantoin rings linked through the *C*-5 and *N*-1 positions, and was called by Gabriel diphenyl hydantil.

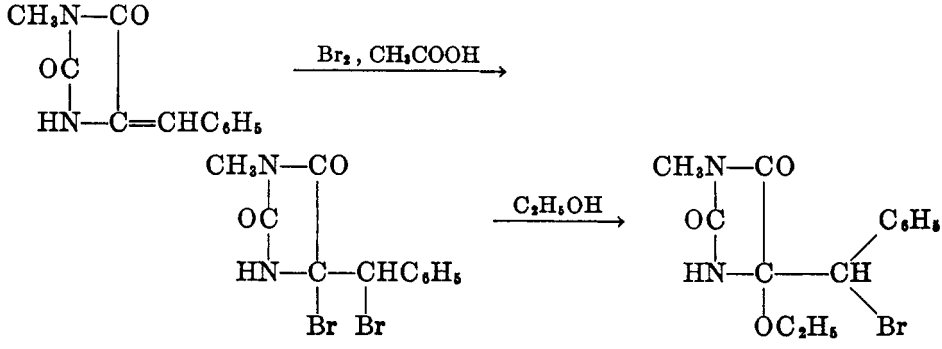


When 5-bromo-5-phenylhydantoin is treated with the sodium derivative of 5-ethylbarbituric acid, there is obtained a 5-barbituric acid derivative of 5-phenylhydantoin (543).

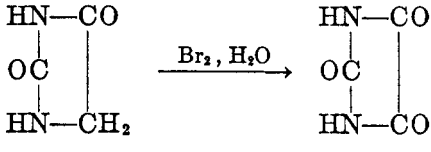
When *C*-5 unsaturated hydantoins are treated with bromine, the primary addition products are unstable and tend to lose hydrogen bromide to form brominated unsaturated hydantoins (285, 435, 448, 630). This behavior was first noted by Wheeler, Hoffman, and Johnson (630), who found that chlorine acted in a similar manner with benzalhydantoin, but that iodine did not react with this hydantoin.



Studies on the bromination of several derivatives of 5-benzalhydantoin showed that in the presence of alcohol the unstable dibromo addition product, which could be isolated when the bromination was carried on in glacial acetic acid (448), reacted to form a bromo-ether (285, 448). For example,



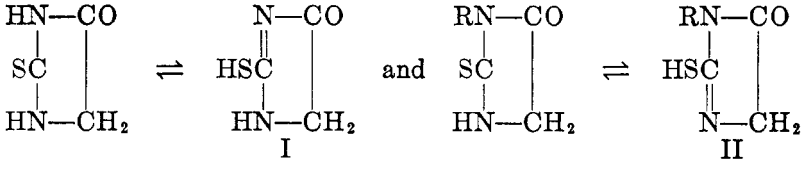
Bromine has also been used to oxidize hydantoin to parabanic acid (565); the hydantoin was heated with bromine water in a sealed tube in order to effect this oxidation.



Substitution in the *C*-5 position increases the resistance of hydantoins to oxidation (40, 41); it was found by Biltz that 5,5-diphenylhydantoin could be recrystallized from boiling concentrated nitric acid (53).

C. Reactions involving the C-2 and C-4 positions

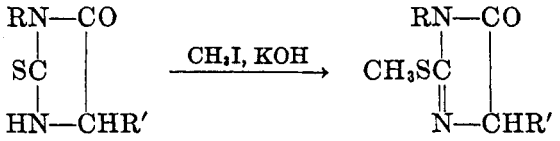
The reactions of 2-thiohydantoins and of 2,4-dithiohydantoins with alkylating agents result in the formation of 2-alkylmercapto derivatives. The corresponding oxygen compounds do not normally react to form 2-enol derivatives, but undergo alkylation on nitrogen atoms only. The formation of 2-alkylmercaptohydantoins indicates that 2-thiohydantoins must exist in tautomeric forms:



For reasons which are discussed later (see Section VI, B, p. 450 ff.), 2-thiohydantoins which are unsubstituted in the *N*-3 position are assumed to react in accordance with structure I, while *N*-3 alkyl or aryl 2-thiohydantoins must assume structure II.

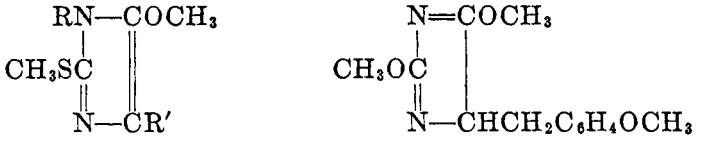
Such 2-alkylmercapto derivatives were first obtained by Marckwald, Neu-

mark, and Stelzner (454) as the result of the action of methyl iodide in alcoholic potassium hydroxide on a series of *N*-3-aryl hydantoins.



Monomethyl derivatives of a number of other 2-thiohydantoins have been obtained through the action of methyl iodide or of dimethyl sulfate (54, 115, 116, 407).

While dimethyl derivatives of *N*-3-aryl-2-thiohydantoins (454) and a trimethyl derivative of *p*-hydroxybenzylhydantoin (557) have been reported and assigned the structures:

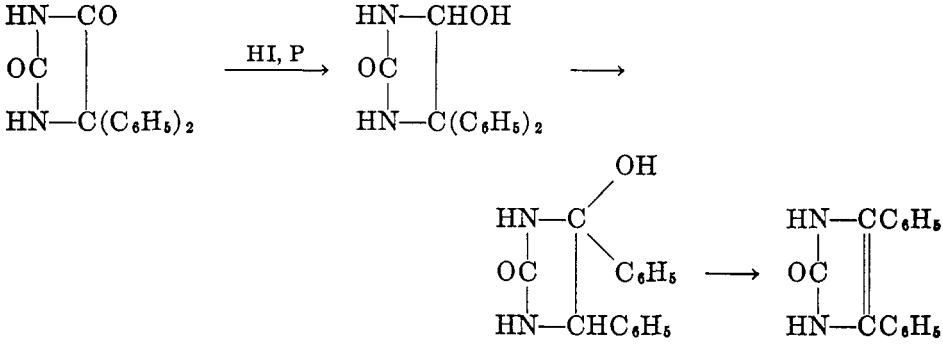


later work indicates that both were probably incorrectly formulated. Johnson and Nicolet were unable to obtain a corresponding dimethyl derivative of 2-thio-5-benzalhydantoin, but instead found that the second methyl group entered the *N*-3 position (379). The second methyl group introduced into 5,5-diphenyl-2-thiohydantoin was found to be in the *N*-1 position (115), while the dimethyl derivative of an *N*-3 substituted 2-thiohydantoin was found to be a 2-methylmercapto-5-methylhydantoin (588).

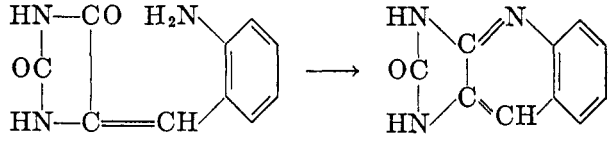
Since 2-thiohydantoins are often more readily prepared and give better yields of the aldehyde condensation products, it is frequently desirable to prepare a 2-thiohydantoin and then desulfurize it to obtain the corresponding oxygen compound. The desulfurization of 2-thiohydantoins was first investigated by Bailey (30, 34), who found that mercuric oxide was not very satisfactory for this purpose, and that the desulfurization of 5,5-disubstituted 2-thiohydantoins was effected much more readily through the action of bromine water. This reagent could not be used with 2-thiohydantoins having one or two hydrogen atoms in the *C*-5 position, since these atoms were then replaced by bromine. Biltz found that 5,5-disubstituted 2-thiohydantoins could be desulfurized through the action of other oxidizing agents, such as alkaline potassium permanganate, dilute nitric acid (54), or sodium hypochlorite (60); these reagents were ineffective, however, if the hydantoin carried substituents on both nitrogen atoms. It was discovered by Johnson, Pfau, and Hodge (383) that chloroacetic acid was an excellent reagent for the desulfurization of 2-thiohydantoins, reacting smoothly with all compounds which were tested. Another method is to treat the 2-alkylmercapto derivative with aqueous or alcoholic hydrogen chloride (115, 116, 627); treatment of thiohydantoins with ammoniacal hydrogen peroxide (349) or with concentrated sodium hydroxide followed by ferrous sulfate (125) will also result in their desulfurization.

For the removal of the sulfur atom in the *C*-4 position of 2,4-dithiohydantoins, in order to prepare the corresponding 2-thiohydantoins, 20 per cent hydrochloric acid was found to be an effective reagent (113). The dithiohydantoins were also found to react with ammonia, hydrazine, or ethanolamine to form 4-imino derivatives; the latter were hydrolyzed to form 4-oxo-2-thiohydantoins. Both of the sulfur atoms of 2,4-dithiohydantoin were removed by treatment with ammoniacal hydrogen peroxide (349). The reverse reaction, that of the conversion of hydantoins into 2,4-dithiohydantoins, may be accomplished through the use of phosphorus trisulfide in tetralin (317).

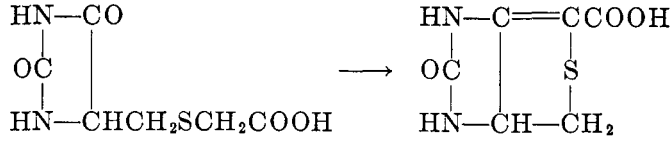
While Biltz experienced great difficulty in his attempts to reduce 5,5-diphenylhydantoin, it was found that reduction, involving first hydrogenation of the carbonyl group in the 4-position followed by a reverse pinacolone rearrangement, took place when the hydantoin was heated with hydrogen iodide and red phosphorus in a sealed tube at 180°C. (79).



The oxygen in the *C*-4 position has been shown to take part in reactions with amino groups, since 5-(2-aminobenzal)hydantoin was found to be converted spontaneously into a hydantoin derivative of quinoline (411, 472).



This same oxygen atom was found to be involved in the dehydration of the carboxymethyl thioether of 5-(mercaptomethyl)hydantoin (106, 107).

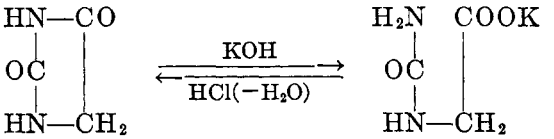


V. THE HYDANTOIN RING

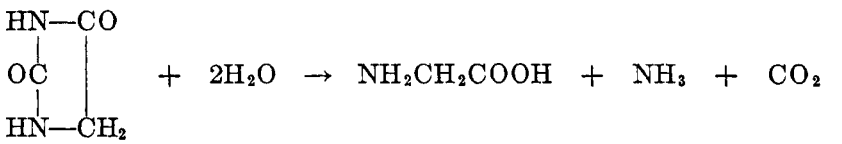
A. The interconversion of hydantoic acids and hydantoins

As the result of investigations extending over many years, the relationship between the cyclic and acyclic ureides has been clarified, so that it is now known

that the former are stable in the presence of dilute aqueous hydrochloric acid but are readily converted into the latter under the action of dilute alkali; the reverse reaction is brought about by treatment with dilute mineral acid.



Neither transformation results in the disruption of the urea grouping. If, however, either product is heated for any considerable period of time in the presence of concentrated mineral acid or of alkali, hydrolysis involving the fixation of an additional molecule of water (or of base) takes place, in which case the reaction is not reversible.



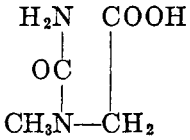
The procedure most commonly followed in the preparation of hydantoins from hydantoic acids is that of Mouneyrat (468); the hydantoic acid is heated with 20 per cent hydrochloric acid for approximately half an hour, and is quantitatively converted into the corresponding hydantoin. It was observed by Bailey (30) that the cyclization of hydantoic acid could also be brought about by heating with hydrogen chloride in ethanol; if the reactants were not heated, the ethyl ester of hydantoic acid was obtained.

There have been a few instances in which cyclization of hydantoic acids has been brought about by treatment with mild alkaline reagents. It was shown by Bailey that, although alcoholic potassium hydroxide will convert ethyl hydantoate into its potassium salt, sodium ethoxide in ethanol will bring about its transformation into hydantoin (30). The same reagent has been used for the conversion of the ureido derivatives of two imino dibasic acids, iminodiacetic acid (38) and phenylalanine-*N*-acetic acid (558), into their hydantoin derivatives. Another mildly alkaline reagent which may be used to effect ring closure is alcoholic ammonia (289).

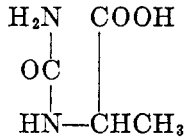
Before it was discovered that heating with mineral acid is the most effective means of bringing about cyclization, hydantoins were generally obtained from the hydantoic acids or esters by heating these compounds without solvent at temperatures between 100° and 150°C. For example, in his synthesis of 5-methylhydantoin from alanine, Urech heated the hydantoic acid obtained by the action of potassium cyanate on alanine at 140°C. until no more water was evolved (608). This same method of closing the ring was used with a number of other hydantoic acids and esters (43, 341, 361, 546, 607). The fact that hydantoins, and not hydantoic acids, are usually obtained when urea is melted with α-amino acids (11, 203, 205, 299, 342, 555) may be explained by assuming that hydantoic acids are first formed and are then converted into their cyclic anhydrides at temperatures above 135°C., the melting point of urea. Probably Aschan's in-

ability to isolate the intermediate phenylthiohydantoic acids from the reaction of phenyl isothiocyanate with several α-amino acids (20) may similarly be accounted for by his experimental procedure of heating the amino acids with phenyl isothiocyanate at a temperature of 140°C. The relatively high temperatures necessary to effect this conversion of hydantoic acids into hydantoins cause a certain amount of decomposition, so that small yields of the hydantoins are frequently obtained. This was clearly demonstrated by Harries and Weiss in the case of ethyl hydantoate (290, 291). Heating of the dry ester at 135°C. for 7 hr. gave only a 60 per cent yield of hydantoin, while quantitative yields were obtained when the ester was warmed for three-quarters of an hour with 25 per cent hydrochloric acid.

The ease with which hydantoic acids or their esters are converted into the corresponding cyclic anhydrides, or hydantoins, is affected by substituent groups on either of the nitrogen atoms, and to a lesser degree by substitution on the alpha carbon atom. Hydantoic acids derived from *N*-substituted α-amino acids are frequently so unstable that they cannot be isolated, or they may undergo rapid cyclization during recrystallization from water. This behavior is illustrated by a comparison of the isomeric hydantoic acids derived from sarcosine and from alanine.



Sarcosine hydantoic acid

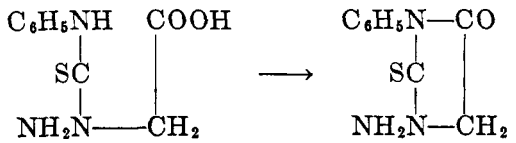


Alanine hydantoic acid

Dakin found that alanine hydantoic acid could be recrystallized from hot water without any chemical change (170), while several investigators commented on the ease with which sarcosine hydantoic acid is converted into the corresponding hydantoin (43, 246). The heating of aqueous solutions of this acid, even for very short periods of time, brings about appreciable cyclization. While it has been reported that hydantoic acid (263) and the phenylureido derivatives of alanine (413) and of phenylalanine (229) may be recrystallized from hot water without change, cyclization of ureido or of phenylureido derivatives of *N*-substituted α-amino acids takes place so readily that it is in certain cases impossible to isolate the free hydantoic acids. Among these are hydantoic acids obtained by the action of potassium cyanate on *N*-phenylglycine (555), *N*-ethylalanine (203), and β-phenylalanine-*N*-acetic acid (278), and the phenylureides of sarcosine and of other *N*-methyl α-amino acids (243), as well as of *N*,*N*′-dimethylcystine (86), tyrosine-*N*-acetic acid (619), and β-phenylalanine-*N*-acetic acid (558). While the esters of these unstable substituted hydantoic acids may usually be isolated, heating in water (619) or even recrystallization from alcohol (301, 601) may bring about their cyclization.

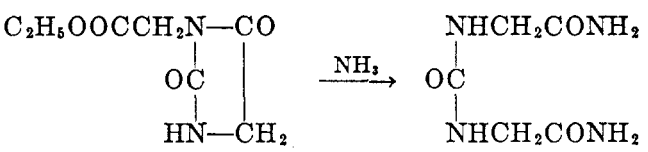
While the thiohydantoic acids and 2-thiohydantoins have many properties in common with their oxygen analogs, it has been found that the ethyl ester of thiohydantoic acid does not undergo cyclization to form 2-thiohydantoin, either

when heated without solvent or when treated with hydrochloric acid (290, 291). The influence of substituent groups on the ease of cyclization is again illustrated by the observations that the phenylthiocarbamido derivative of hydrazinoacetic acid is converted into 1-amino-2-thio-3-phenylhydantoin in boiling water (602),

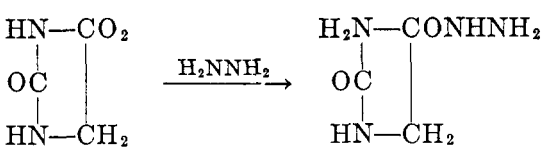


that the free thiohydantoic acids obtained by the action of phenyl isothiocyanate on a number of α-amino acids in alkaline solution were unstable and were converted into the corresponding 2-thiohydantoins when the reaction mixture was neutralized (98), and that 2-thiohydantoin-3-acetic acid was obtained when the ethyl ester of the corresponding thiohydantoic acid was treated with acid (384). The presence of an acyl group on either of the nitrogen atoms of thiohydantoic acid has been shown by Johnson (377, 385, 631) to allow cyclization to the 2-thiohydantoin to take place.

The reagent most commonly used to convert hydantoins into the corresponding hydantoic acids is aqueous barium hydroxide. This was first used by Baeyer in the preparation of hydantoic acid from his newly discovered hydantoin (27). Under the action of boiling barium hydroxide solution, hydantoin was converted into the barium salt of hydantoic acid. Other reagents which have been used for this purpose include alcoholic potassium hydroxide (413), aqueous sodium or potassium hydroxide (255, 629), aqueous or alcoholic ammonia (260, 439), and hydrazine (232). As will be shown later, long periods of heating with metallic hydroxide in aqueous solution lead also to a more profound breakdown of the hydantoins. The action of ammonia, either in alcoholic solution or in concentrated aqueous solution, has been shown to convert ethyl 3-hydantoinacetate into the diamide of carbamidodiacetic acid (260, 439).



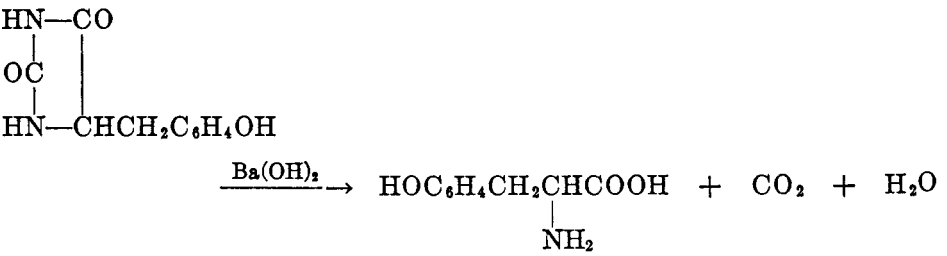
Hydrazine was found to react with hydantoin, as well as with ethyl hydantoate, to form the hydrazide of hydantoic acid (232).



B. Hydrolysis of hydantoins to form amino acids

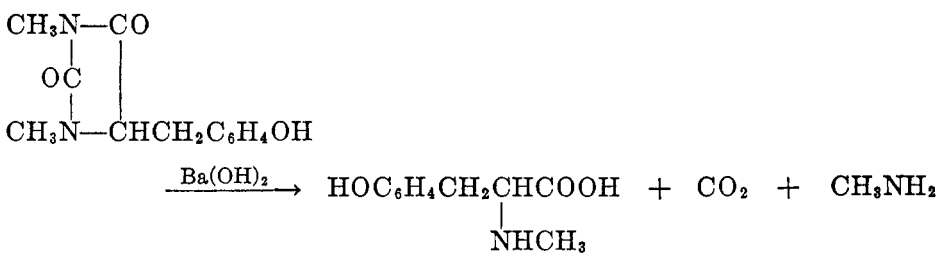
When hydantoins are heated for relatively long periods of time with a large excess of barium hydroxide in aqueous solution, a more profound breakdown than

that of hydantoic acid formation takes place, and α-amino acids are obtained. This property of hydantoins has been of very great value in the synthesis of α-amino acids which are difficult to obtain by other methods. The hydantoin synthesis of α-amino acids was first suggested as a general method by Wheeler and Hoffman (629), and was used by them in the syntheses of phenylalanine and of tyrosine. In the preparation of tyrosine, for example, 5-*p*-hydroxybenzylhydantoin, obtained through the reduction and demethylation of the condensation product of anisaldehyde and hydantoin, was hydrolyzed in aqueous barium hydroxide and, after the removal of the barium as barium sulfate, tyrosine was obtained in excellent yields.

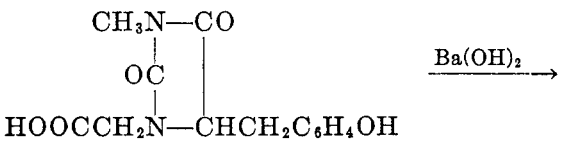


This general method has been used by Johnson and his associates to prepare a number of substitution products of β-phenylalanine. Many other α-amino acids have been prepared through the hydrolysis of appropriately substituted hydantoins (see table 6). The necessary *C*-5 substituted hydantoins are generally obtained either through the condensation of aldehydes with hydantoins, or through the Bucherer–Bergs synthesis from carbonyl compounds.

When an *N*-1 substituted hydantoin is subjected to intensive hydrolysis of this type, the amino acid obtained bears this same substituent on the amino nitrogen. For example, Johnson and Nicolet (378) prepared *N*-methyltyrosine through the hydrolysis of 1,3-dimethyl-5-*p*-hydroxybenzylhydantoin:



This same principle was first applied by Hahn and Renfrew (286) to the synthesis of imino dibasic acids. When *N*-3-methyl-5-*p*-hydroxybenzylhydantoin-*N*-1-acetic acid was hydrolyzed with barium hydroxide, the *N*-acetic acid derivative of tyrosine was formed:



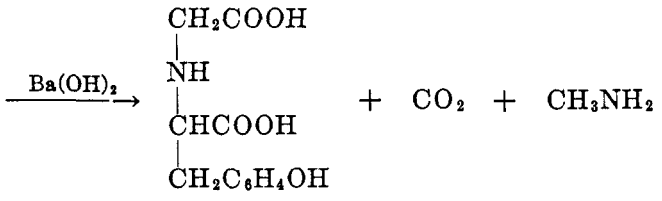


TABLE 6

Amino acids prepared from hydantoins

AMINO ACIDS	REFERENCES	AMINO ACIDS	REFERENCES
Alanine	(252)	6-Methoxytryptophan	(292)
β-(3-Aminophenyl)alanine	(320)	α-Methylaspartic acid and derivatives	(500, 501, 502, 503)
α-Aminoisobutyric acid	(606, 607)		
α-Aminopelargonic acid	(359)		
α-Aminophenylacetic acid derivatives	(293)	β-(*p*-Methyl-*p'*-diphenyl-sulfide)alanine	(417)
2-Amino-5-phenyl-3-pentenoic acid	(391)	1-Methylhistidine	(545)
		N-Methylphenylalanine	(280)
β-(2-Chlorophenyl)alanine	(320)	(Amino)*N*-methyltryptophan	(257, 463)
3,5-Dichlorotyrosine	(630)	3-Methyltryptophan	(257, 524)
β-(2,4-Dihydroxyphenyl)-alanine	(183)	*N*-Methyltyrosine	(378)
β-(3,4-Dimethoxyphenyl)-alanine	(365)	α-Phenoxymethyl-β-phenyl-alanine and derivatives	(498, 499, 504)
β-Furylalanine	(182)		
α-Furylaminoacetic acid	(293)	β-Phenylalanine	(629)
Glycine	(407)	β-Piperonylalanine	(184)
β-(*p*-Hydroxy-*p'*-diphenyl-sulfide)alanine	(417)	β-Pyridylalanine	(483)
		β-Quinolylalanine	(505)
Hydroxyglutamic acid	(171)	β-2-Thienylalanine	(39, 202)
β-(Hydroxymethylfuryl)-alanine	(344)	Thiotyrosine	(367)
		β-(Trihydroxyphenyl)-alanine	(549)
Lysine	(251)		
Methionine	(114, 253, 436, 508)	β-(Trimethoxyphenyl)-alanine	(351, 591)
		Tryptophan	(96, 100, 206, 437, 452)
Methionine, selenium analog	(401)		
β-(3-Methoxy-4-hydroxy-phenyl)alanine	(365)	Tyrosine	(629)
		o-Tyrosine	(387)
β-(4-Methoxy-3-hydroxy-phenyl)alanine	(186)		

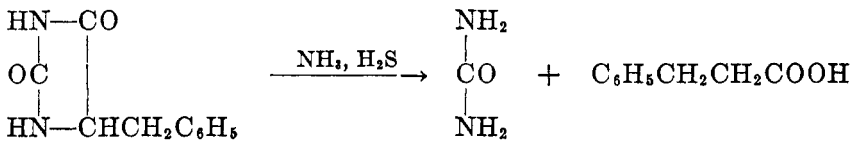
Through the hydrolysis of appropriately substituted hydantoins, other imidodiacetic acids have been prepared by D. A. Hahn and her associates, including tyrosine-*N*-phenylacetic acid (275), and the *N*-acetic and *N*-phenylacetic acid derivatives of β-phenylalanine (283).

Other methods of hydrolysis of hydantoins than with metallic hydroxides have been used. It was discovered by Boyd and Robson (95) that hydantoins may be converted into α-amino acids through hydrolysis with aqueous ammonium sulfide, a method which has been used frequently and which is desirable

when the resulting amino acid is readily susceptible to oxidation. Acids have also been used to effect this conversion. The first preparation of an α-amino acid from a hydantoin was reported by Urech (607), who heated 5,5-dimethylhydantoin in a sealed tube with concentrated hydrochloric acid at a temperature of 150–160°C. and obtained α-aminoisobutyric acid; Komatsu used a similar method to obtain glycine from 2-thiohydantoin (407). Wheeler and Hoffman had observed that appreciable amounts of tyrosine were formed during the reduction and demethylation of 5-anisalhydantoin with hydrogen iodide and red phosphorus; upon further investigation it was found that 5-*p*-hydroxybenzylhydantoin was completely converted into tyrosine after heating for 9 hr. with hydriodic acid in the presence of iodine (629). Hydantoins have also been hydrolyzed to form α-amino acids by heating with 60 per cent sulfuric acid for several hours at 130°C. (105), by treating with tin and hydrochloric acid (382), and by refluxing with a mixture of acetic acid and hydrogen chloride (114).

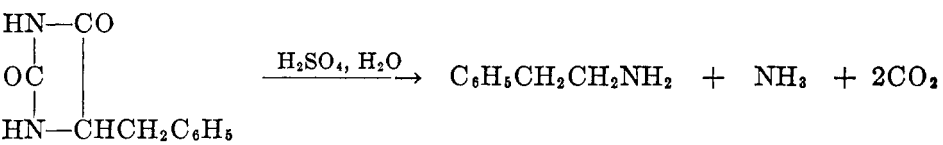
C. Hydrolysis of hydantoins to form products other than amino acids

Two unusual types of hydantoin hydrolysis have been reported by Wada, but his results have not been confirmed by other investigators. It was stated that when hydantoins were dissolved in dilute aqueous ammonia and hydrogen sulfide led into the hot solution, the hydantoins were decomposed into urea and saturated acids; for example, that 5-benzylhydantoin was converted quantitatively into β-phenylpropionic acid and urea (614, 616).



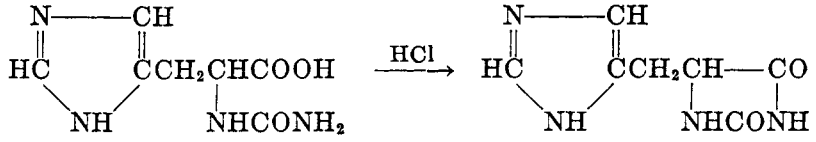
The quantitative formation of urea as a result of this reaction is quite unexpected in view of the work of Boyd and Robson (95), who found that aqueous ammonium sulfide would convert hydantoins into α-amino acids. Wada also reported that a reductase, present in milk, blood, and the pancreas, would split hydantoins to form urea (615).

According to Wada, the action of concentrated acid or alkali on hydantoins will convert them into the corresponding amines (613). The reagents used included concentrated hydrochloric acid, 30 per cent sulfuric acid, and saturated barium hydroxide solution. It was stated that when 5-benzylhydantoin was refluxed for 10 hr. with 30 per cent sulfuric acid, β-phenethylamine was obtained in 80 per cent yields.

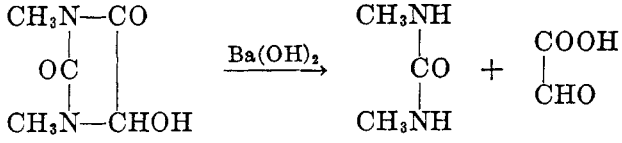


This type of hydantoin degradation was suggested as a means for the decarboxylation of α-amino acids, through preparation of their hydantoin derivatives

and subsequent hydrolysis according to the above scheme; it was also recommended for the preparation of β-amino and γ-amino acids, since 5-hydantoinacetic acid would be converted into β-alanine, while 5-hydantoinpropionic acid would give γ-aminobutyric acid. It was found by Shchukina that this method was not effective for the conversion of histidine into histamine (562). Histidine was transformed into the corresponding hydantoic acid through the action of urea, but treatment of the hydantoic acid with concentrated hydrochloric acid led to the formation, not of histamine, but of 4-(5-hydantoylmethyl)imidazole.

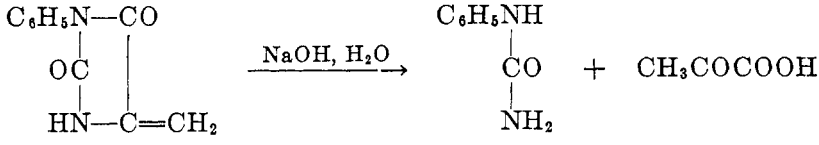


When the carbon atom in the *C*-5 position of a hydantoin is linked to another atom through a double bond, or when there is a hydroxyl group in the *C*-5 position, alkaline hydrolysis of the hydantoin may lead to the production of an α-keto acid and urea, or of ammonia, carbon dioxide, oxalic acid, and a hydrocarbon. This type of hydrolysis was first observed by Andreasch (8), who found that the hydrolysis of 1,3-dimethyl-5-hydroxyhydantoin with barium hydroxide produced dimethylurea and glyoxylic acid:



The dimethylurea was further hydrolyzed to methylamine and carbon dioxide, while the glyoxylic acid underwent a Cannizzaro reaction to form oxalic acid and glycolic acid.

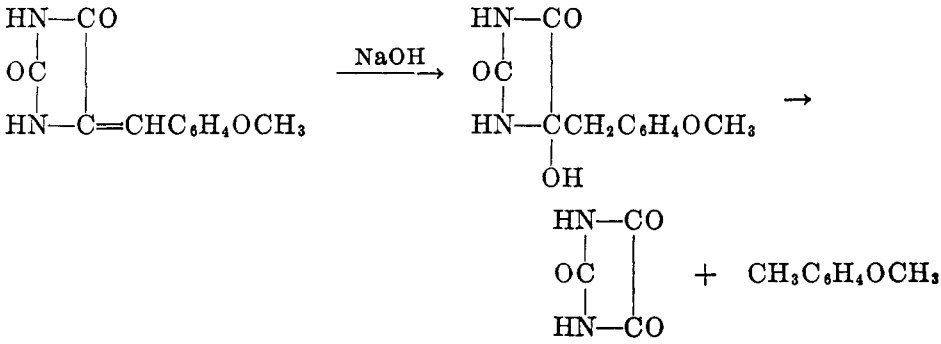
Wheeler and Hoffman (629) found that, while 5-anisalhydantoin is reprecipitated unchanged by the addition of acid to its solution in cold alkali, boiling of this hydantoin in alkaline solution results in the formation of *p*-methoxyphenylpyruvic acid. It was shown by Bergman and Delis that 3-phenyl-5-methylenehydantoin is hydrolyzed by normal aqueous sodium hydroxide to give pyruvic acid and phenylurea (47).



Under similar conditions, 3-phenyl-5-benzalhydantoin was converted into phenylpyruvic acid and phenylurea. This same type of decomposition of unsaturated hydantoins has also been observed by other investigators (12, 249, 551).

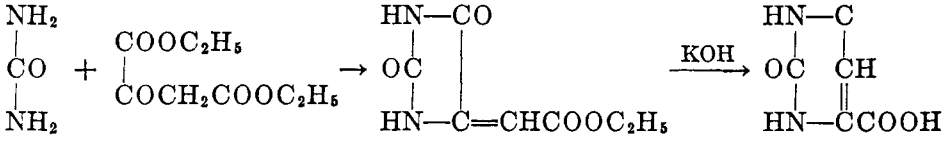
The mechanism of this type of decomposition was studied by Henze, Whitney, and Eppright (320), who found that with more concentrated alkali, as with 5 per cent sodium hydroxide, α-keto acids were not formed, but instead oxalic

acid and a hydrocarbon. The hydrolysis of 5-anisalhydantoin under these conditions produced some *p*-methoxyphenylpyruvic acid, but chiefly *p*-methoxytoluene and oxalic acid. They suggest the following series of reactions:



The parabanic acid resulting from the splitting off of *p*-methoxytoluene would then be hydrolyzed to form oxalic acid, ammonia, and carbon dioxide. An alternate mechanism would postulate the formation of *p*-methoxyphenylpyruvic acid, which was found to be hydrolyzed by barium hydroxide to form *p*-methoxytoluene and oxalic acid. These authors suggest that in the work of Wheeler and Hoffman (629) the barium hydroxide solution was too dilute to carry the reaction farther than to the α-keto acid, and do not agree with the conclusion of Nicolet and Campbell (482) that unreduced hydantoins are difficult to hydrolyze.

The action of potassium hydroxide solution on the unsaturated hydantoin derivative obtained by the reaction of urea with oxalacetic ester was found to convert this hydantoin into a pyrimidine derivative, orotic acid or 4-uracilcarboxylic acid (464, 489). Since no intermediates were isolated, the mechanism of the reaction is not certain.



A similar rearrangement of a homolog of the above hydantoin to form 4-thyminecarboxylic acid has also been reported (459).

D. Substituents and the stability of the hydantoin ring

It may be stated as a general rule that substituted hydantoins are much more stable than unsubstituted hydantoins, both from the standpoint of ease of formation from the corresponding hydantoic acids and with respect to their stability in the presence of various hydrolytic or oxidizing agents. This increase in stability may be brought about by substituent groups on either of the nitrogen atoms, as well as on the carbon atom in the *C*-5 position.

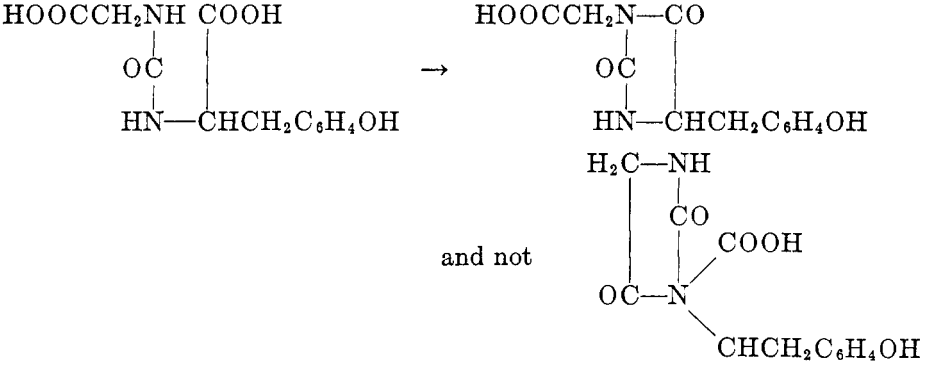
Substitution in the *N*-1 position is particularly effective in this regard. This

is clearly illustrated by the greater ease with which hydantoic acids derived from *N*-1 substituted hydantoins undergo cyclization (see previous discussion, Section V, A). The presence of substituent groups on both of the nitrogen atoms appears to increase further the stability of the hydantoin: while it is possible to isolate the ureido acid of sarcosine (43, 546), the phenylureido derivative of sarcosine undergoes cyclization so rapidly that only the phenylhydantoin can be obtained (243). The stability toward alkali of 3-phenylhydantoin and of 1-methyl-3-phenylhydantoin was studied by Gatewood (249), who found that the latter was attacked far more slowly by aqueous alkali.

The presence of a substituent in the *N*-3 position alone also increases the stability of the resulting hydantoin, since phenylthiocarbamido derivatives of α-amino acids readily undergo cyclization to form 3-phenyl-2-thiohydantoins (98), while ethyl thiohydantoate cannot be converted into 2-thiohydantoin either by heating or by treatment with hot 25 per cent hydrochloric acid (290). The greater stabilizing effect of *N*-1 substitution is shown by the fact that 1-hydantoinacetic acid has been found to be more resistant to hydrolysis with aqueous ammonia than the isomeric 3-hydantoinacetic acid (118, 394).

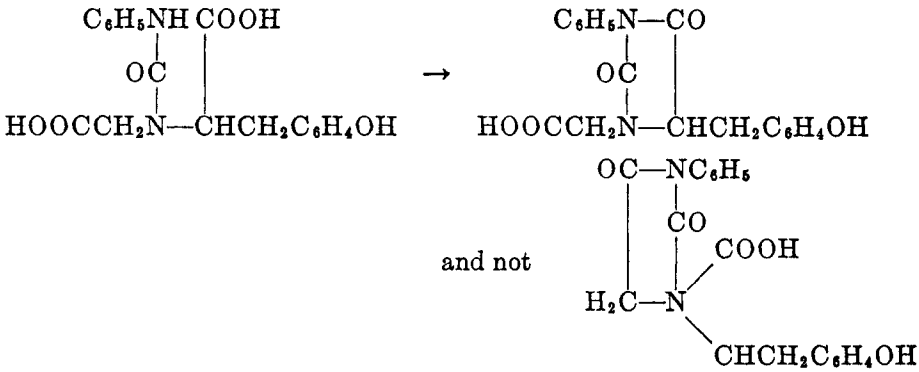
A comparative study of a series of 5-substituted hydantoins with respect to their resistance to alkaline hydrolysis has been made (343); in order of increasing stability, these hydantoins were 5,5-cyclopropanespirohydantoin, hydantoin, 5,5-cyclobutanespirohydantoin, 5-methylhydantoin, 5,5-dimethylhydantoin, and 5,5-diethylhydantoin. Substitution in the *C*-5 position was also found to affect the rate of catalytic oxidation (41); the hydantoins studied were, in order of decreasing rates of oxidation and therefore increasing stability, 5-phenylhydantoin, hydantoin, 5-methylhydantoin, 5-benzylhydantoin. It was found, furthermore, that disubstitution in the *C*-5 position inhibited oxidation under the conditions employed. The observation that 5-methylhydantoin is formed more rapidly than is hydantoin through the acid hydrolysis of glycyl derivatives of hydantoic acids also indicates that substitution in the *C*-5 position increases the stability of a hydantoin (160).

Further evidence for the effect of *C*-5 substituents on the stability of hydantoins as indicated by ease of cyclization is given by the behavior of several hydantoic acids which theoretically might undergo ring closure to give either of



two isomeric hydantoins. In each of these cases, one isomer would carry a substituent on the *C*-5 carbon atom while the other would not, and it was found in each instance that it was the *C*-5 substituted isomer which was formed. Johnson and Hahn found that the hydantoic acid derived from 5-*p*-hydroxybenzylhydantoin-3-acetic acid by treatment with dilute alkali underwent cyclization to give only the original hydantoin and not the isomeric hydantoin-3-*p*-hydroxybenzylacetic acid (372)(see page 447).

Johnson and Bates obtained similar results with the hydantoic acid of 5-benzylhydantoin-1-acetic acid (361). The phenylureido derivative of tyrosine-*N*-acetic acid underwent spontaneous ring closure when the solution of its potassium salt was acidified to form only 3-phenyl-5-*p*-hydroxybenzylhydantoin-1-acetic acid, and not the isomeric 3-phenylhydantoin-1-*p*-hydroxybenzylacetic acid (619).



The ureido and phenylureido derivatives of phenylalanine-*N*-acetic acid showed similar behavior (278, 558), except under such conditions that the ureido derivative could react only to form the isomeric hydantoin-1-benzylacetic acid (284).

Unsaturation in the *C*-5 position has been stated to increase the stability of hydantoins to alkaline hydrolysis. Nicolet and Campbell (482) found that 1-methyl-5-benzalhydantoin was more difficult to hydrolyze than 1-methyl-5-benzylhydantoin. Similarly, Ghosh (254) noted that the unsaturated condensation products of 2-thiohydantoin with aldehydes were much more resistant to hydrolysis with alcoholic alkali than was unsubstituted 2-thiohydantoin.

While all hydantoins are more or less unstable in the presence of alkali, the presence of substituents on both of the nitrogen atoms as well as on the *C*-5 carbon atom appears to endow remarkable stability toward acid hydrolysis. Hydantoins bearing a substituent only in the *C*-5 position, such as 5-*p*-hydroxybenzylhydantoin, may be broken down by boiling with concentrated hydriodic acid (629), while a 3,5-disubstituted hydantoin, 5-benzylhydantoin-3-acetic acid, was hydrolyzed with concentrated hydrochloric acid at 145°C. (361). However, all attempts to hydrolyze the trisubstituted hydantoin, 3-methyl-5-*p*-hydroxybenzylhydantoin-1-acetic acid, in acid solution met with negative results (286). Hahn and Renfrew were able to recover this hydantoin completely unaltered after heating either with concentrated hydrochloric acid or with hydriodic acid and red phosphorus at 200°C. for 6–8 hr.

VI. OTHER CHEMICAL AND PHYSICAL PROPERTIES OF HYDANTOINS

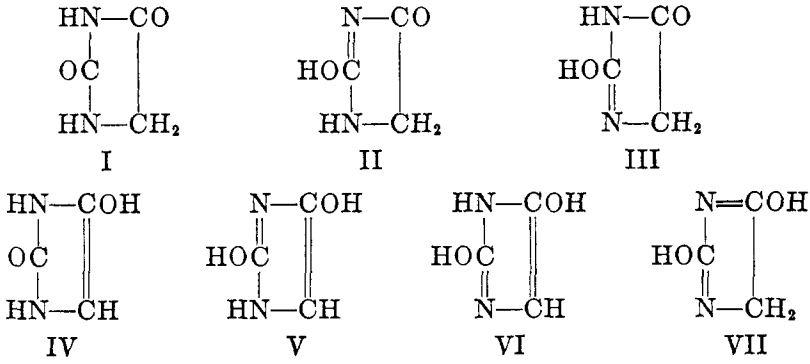
A. Physicochemical properties

While most of the studies of hydantoins have been purely chemical, certain of their physical properties, especially their dissociation constants and absorption spectra, have been investigated in some detail. Thermochemical data on hydantoic acid and hydantoin have been obtained (457), their dielectric constants determined (156, 188), and their solubilities in various solvents studied (154, 449, 450). The dissociation constant of hydantoin, 7.59×10^{-10} (604, 635), shows that it acts as a weak acid of approximately the same strength as phenol or hydrocyanic acid. Dissociation constants of substituted hydantoins have also been obtained (212, 507, 638); these have been found useful in the interpretation of certain properties of hydantoins and are discussed elsewhere in this paper (see Section VI, B).

Absorption spectra studies on hydantoin and certain of its derivatives were first made by Asahina (18, 19). Such data have been found of value in detecting substitution in the *N*-1 position of a hydantoin (110, 560), and in assigning the correct formulae to certain hydantoin derivatives (588, 589). The absorption spectra of a number of substituted hydantoins have been studied by D. A. Hahn and her associates (276, 280, 281, 284, 285, 448, 560); these show clearly the effect of substitution in the ring and of unsaturation in the *C*-5 position. Absorption spectra of 3-methyl-5-benzalhydantoin and of its 1-phenyl derivative have been determined and found similar to that of a degradation product of gliotoxin (200).

B. Tautomeric forms of hydantoins

Certain reaction of hydantoins have been explained by the existence of tautomeric forms of the hydantoin molecule. The different formulations, involving both amido-imidol and keto-enol tautomerism, which have been suggested include numbers I–VII.

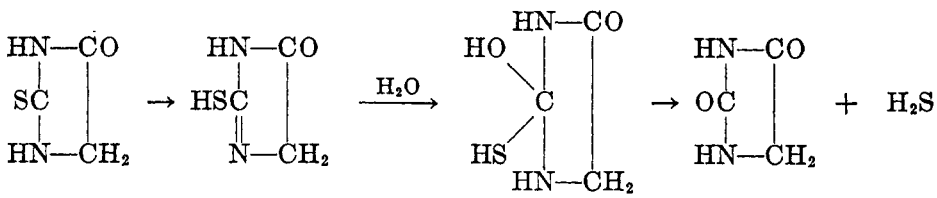


Certain of these formulations, especially II and III, are of particular value in explaining the reactions of 2-thiohydantoins; IV, V, and VI, which involve enolization between the 4- and 5-positions, have been used to account for the

racemization of optically active hydantoins with an asymmetric *C*-5 carbon atom.

It seems probable that 2-thiohydantoins readily assume form II, since the alkylation of 2-thiohydantoins results in the formation of 2-alkylmercapto derivatives (54, 115, 116, 379, 407, 566). The observation of Asahina (19) that the absorption spectrum of 2-thiohydantoin is entirely unlike that of hydantoin indicates that they differ in structure, quite possibly as I and II. The fact that 5-*sec*-butylhydantoin does not give a test for the C=N grouping may also indicate that hydantoins do not normally exist in forms II or III (90), although it has been reported that copper and nickel salts of 5,5-diphenylhydantoin, corresponding to formula II or III, can be obtained (594, 595).

It was suggested by Komatsu (408) that the desulfurization of 2-thiohydantoins involved reaction in form III.

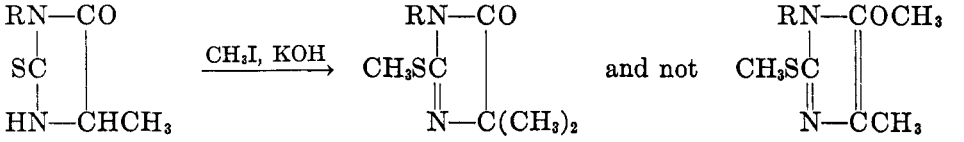


The fact that it is impossible to desulfurize 1,3-dimethyl-2-thio-5,5-diphenylhydantoin, which cannot exist in either form II or form III, with reagents which might be expected to oxidize a thiol group, while 2-thio-5,5-diphenylhydantoin and its 3-methyl derivative are readily desulfurized by these reagents, is evidence for the existence of 2-thiohydantoins in form II or form III (54).

When there is an unsubstituted hydrogen atom in the *N*-3 position, formulation II is to be preferred to III, since a number of studies have indicated that the *N*-3 hydrogen is the hydrogen atom responsible for the weakly acidic nature of hydantoin. It has been shown that hydantoin and 5,5-dimethylhydantoin have nearly identical dissociation constants, unlike the corresponding barbituric acid derivatives, and that therefore the ionizing hydrogen comes from one of the NH groups and not from the CH_2 group (638); similar results have been obtained with hydantoin and 5,5-diphenylhydantoin (212). Pickett and McLean (507) found that hydantoin and 5-benzylhydantoin were weakly acidic, while 3-methyl-5-benzylhydantoin showed no acidic properties, indicating that the *N*-3 hydrogen atom was the acidic hydrogen in the hydantoin molecule. Further confirmation of this conclusion was furnished by Stuckey (589): the absorption spectra of a series of substituted hydantoins were studied, and it was found that hydantoins having a hydrogen atom in the *N*-3 position showed a shift in the absorption maximum toward the red end of the spectrum in alkaline solution, while *N*-3 substituted hydantoins did not show such an alkaline shift.

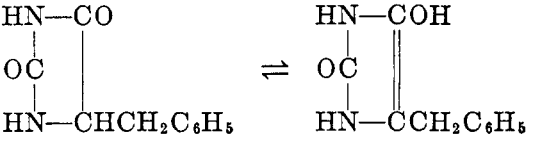
The fact that *N*-3 substituted hydantoins will also form 2-alkylmercapto derivatives (54, 454, 588) indicates that formulation III is also possible. It has been reported that dialkyl derivatives, presumably corresponding to formulation VI, could be obtained from *N*-3 substituted 2-thiohydantoins (454),

but absorption spectra studies by Stuckey (588) of the methylated products of 3,5-disubstituted 2-thiohydantoins indicate that the second methyl group enters the *C*-5 position, since the product does not have a conjugated double bond system.



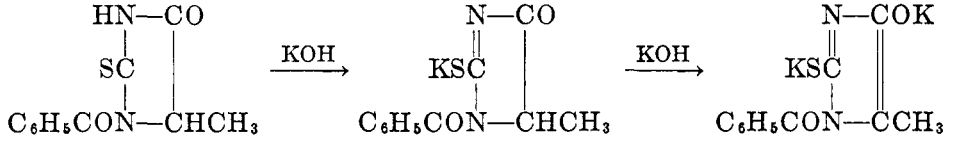
It was suggested by Ghosh (254) that *N*-1 substituted hydantoins condense much less readily than hydantoins or 2-thiohydantoins which have a hydrogen atom in that position because the former cannot assume the structure III. A double bond between the *N*-1 and *C*-2 atoms might be expected to assist in the activation of the *C*-5 methylene group.

The racemization of optically active 5-benzylhydantoins in dilute alkaline solutions was explained by Dakin through tautomerism of forms I and IV (168, 173):



This conclusion was supported by the fact that 5-ethyl-5-methylhydantoin, which was incapable of keto-enol tautomerism, was not racemized under these conditions. Similar explanations have been offered for the rapid racemization in alkaline solution of other optically active hydantoins (566, 625). It has been suggested that the oxidation of hydantoins may be preceded by enolization of this type, since 5,5-disubstituted hydantoins are not oxidized by reagents effective with hydantoin and with 5-monosubstituted hydantoins (41).

The existence of an enol form corresponding to V was indicated by the work of Sjollema and Seekles (566), who found that it required 2 moles of alkali to racemize 1-benzoyl-2-thio-5-methylhydantoin.



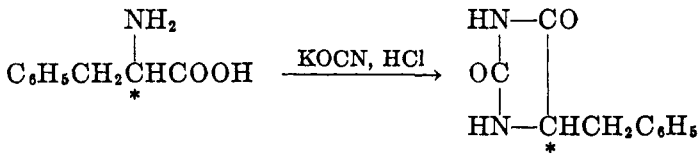
The possibility of the existence of forms V and VI was postulated by Bovarnick and Clarke (92) to explain the racemization of certain hydantoins; these investigators found that a phenyl group in the *N*-3 position increased the rate of racemization.

The formation of a trimethyl derivative of 5-*p*-hydroxybenzylhydantoin was assumed by Scott and Cohen (557) to indicate that this hydantoin reacted in the diimidol form VII. Direct evidence for the existence of any of the imidol-enol or diimidol forms V, VI, and VII is lacking; as already pointed out, spectroscopic

evidence shows that compounds previously assigned the structure VI were incorrectly formulated (588). Only one example of structure VII has been reported, and Johnson and Nicolet (379) were unable to obtain dialkyl derivatives of 2-thio-5-benzalhydantoin corresponding to this formulation.

C. Optical and geometrical isomerism of hydantoin derivatives

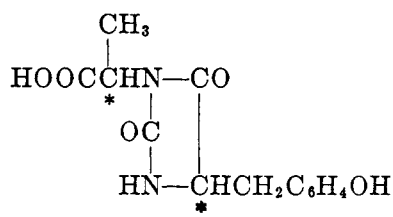
When hydantoins are synthesized from optically active α-amino acids, the esulting hydantoins are also optically active.



• = asymmetric carbon atom.

A number of such optically active hydantoins have been synthesized by Dakin (168, 172, 173) and by Sobotka (571, 573). Racemic mixtures obtained through the synthesis of 5-substituted hydantoins by various methods have been resolved by means of brucine salts (512, 571, 572). It was also reported that when aspergillus was grown on the sodium derivative of nirvanol (5-ethyl-5-phenylhydantoin), the dextro enantiomorph was obtained (572); this modification was found to be a slightly less effective hypnotic than the racemic mixture, but to be only one-third as toxic (574).

The presence of two asymmetric carbon atoms in the hydantoin molecule results in the existence of diastereoisomers which may be separated through differences in their solubilities in various solvents. Such isomers were encountered by Hahn and Gilman (281) for 5-*p*-hydroxybenzylhydantoin-3-propionic acid,



as well as for derivatives of two other hydantoins by D. A. Hahn and her associates. These were 3-methyl-5-*p*-hydroxybenzylhydantoin-1-phenylacetic acid (275, 276) and 3-methyl-5-benzylhydantoin-1-phenylacetic acid (287). Derivatives of 3-hydantoinacetic acid obtained by the action of phosgene on α-amino acids were found to show this same type of isomerism when there were two asymmetric carbon atoms in the molecule; these included the hydantoins prepared from phenylalanine (624, 625) and from alanine (261).

The existence of geometrical isomerism among the *C*-5 unsaturated derivatives of hydantoin has been reported, for those hydantoins which do not carry substituents in the *N*-1 and *N*-3 positions, only for 5-benzalhydantoin (277, 360).

These forms differ in their solubilities and melting points, but on reduction form the same 5-benzylhydantoin. Similarly, two isomers of 1,3-diphenyl-5-benzalhydantoin have been reported (371). Geometrical isomers of a number of different *N*-3 and *N*-1,*N*-3 substitution products of 5-benzalhydantoin and of 5-anisalhydantoin have been prepared and studied by D. A. Hahn and her associates (275, 276, 279, 280, 282, 286, 287). It was discovered by Hahn and Gilman (282) that one isomer of 3-methyl-5-anisalhydantoin-1-acetic acid could be transformed into the other by treatment with hydrogen chloride in alcohol solution.

VII. USES OF HYDANTOINS

A. Hydantoins as medicinal products

A number of 5,5-disubstituted hydantoins have found use in medicine, first as hypnotics, later for the treatment of chorea, and more recently in the treatment of epilepsy. The first hydantoin to be used widely in medicine was 5-ethyl-5-phenylhydantoin, which soon became known as nirvanol. This hydantoin, introduced as a hypnotic in 1916 by Wernecke (623), was reported to have about the same intensity of action as phenobarbital (5-ethyl-5-phenylbarbituric acid) but to be less toxic. Nirvanol was first used in 1919 for chorea by Roeder (525), who reported that it was harmless in infrequent doses. Soon, however, it was found that the continued use of nirvanol led to various toxic symptoms (241, 347, 536); its dangerous nature was reviewed by Jones and Jacobs in 1932 (393).

The hydantoin derivative which has achieved the greatest prominence in medicine is 5,5-diphenylhydantoin, known also under such names as dilantin and epanutin. Its sodium derivative, more frequently employed, is referred to as sodium diphenylhydantoinate, dilantin sodium, phenytoin sodium, or diphantoin. It has also been used in the form of a calcium derivative (88), or combined with sodium bicarbonate under the name of zentropil (14). The use of dilantin in the treatment of epilepsy was first recommended in 1938 by Merritt and Putnam (461); these investigators had tested a number of phenyl derivatives for anticonvulsant action, and had found that diphenylhydantoin was the most effective anticonvulsant with the least hypnotic effect among those tested (515). In studies with a group of two hundred patients, it gave good results in most cases, with only minor toxic symptoms in a few cases. After further clinical tests, chiefly by Kimball (399), it was accepted in 1939 by the American Medical Association for inclusion in its list of new and nonofficial remedies (6).

The advantages of dilantin over other anticonvulsants have been pointed out in review articles by Blair (84) and by Cheymol (143); it is a good antiepileptic, without the hypnotic action of the barbiturates. As with nirvanol, toxic effects are not entirely absent (222, 268, 295). There has been a difference of opinion as to whether the use of dilantin causes an ascorbic acid deficiency (192, 193, 211, 399, 460). Dilantin has also been recommended for use in cases of anoxia resulting from high altitudes (210, 256). Tests made with experimental animals showed that their survival time was markedly increased by treatment

with dilantin before exposure to a pressure of 148 mm. of mercury, corresponding to an altitude of 39,000 feet (210, 256). This drug also increased the tolerance of these animals to decompression (256, 335).

The discovery of the narcotic and hypnotic effects of nirvanol led to the testing of a number of other 5,5-disubstituted hydantoins for similar physiological activity, especially after the toxicity of nirvanol itself had been pointed out. A series of 5,5-dialkyl hydantoins was studied by Lumière and Perrin (445), who found that 5,5-dipropylhydantoin was a good hypnotic with low toxicity; less good were 5-ethyl-5-isobutyl- and 5-propyl-5-isobutyl-hydantoins, while 5,5-diisobutylhydantoin showed little or no activity. Among the 5-phenyl-5-alkylhydantoins, the propyl and isobutyl derivatives were found to approach nirvanol in narcotic activity, while the isopropyl and *n*-butyl derivatives were ineffective (598). Herbst and Johnson found that 5-methyl-5-phenylethylhydantoin was nearly as effective as nirvanol, but only about half as toxic; 5,5-cyclopentamethylenehydantoin was as toxic as nirvanol, and completely ineffective as a hypnotic (324). A series of twenty-nine phenylalkylhydantoins was studied by Novelli (487), who noted that the ethyl and propyl derivatives were effective hypnotics, but that this activity decreased with increase in size of the alkyl group. The phenyl group could not be replaced to advantage either by naphthyl or by phenanthryl groups, substitution in the phenyl group led to unfavorable properties, while reduction of the phenyl group to cyclohexyl destroyed the hypnotic action although it did reduce the toxicity. Diphenylhydantoin was reported to have no narcotic activity.

While dilantin appears to be the hydantoin derivative most generally used in the treatment of epilepsy, many other hydantoins have been tested for their anticonvulsant properties. Among the most promising of these are 5-phenyl-5-phenylethylhydantoin (309), 5-phenyl-5-propoxymethylhydantoin and 5-phenyl-5-isopropoxymethylhydantoin (314, 462), 5,5-diisobutylhydantoin (144), 3-methyl-5-ethyl-5-phenylhydantoin (15), and 5-alkyl-5-(2-thienyl)hydantoins (584). Hydantoins bearing other groups in the *C*-5 position have also been tested; these include alkoxymethyl (462, 522), phenoxymethyl (632), disubstituted aminomethyl (306, 308), alkylthiomethyl and alkylsulfonylmethyl (109, 441, 462). Certain cyclic ketones have also been converted into hydantoins found to have anticonvulsant activity (315, 600). In a series of 5-phenyl-5-alkylthiomethylhydantoins, the most active compound, in which the alkyl group was ethyl, was about one-fourth as active as dilantin (109); the oxidation of the sulfide to the sulfone group usually resulted in a decrease in anticonvulsant activity (441).

A few studies have been made of 5,5-disubstituted 2-thiohydantoins, although such compounds would be expected to be more toxic than the corresponding oxygen compounds. It was shown by Lewis that hydantoin has no toxic effects, while 2-thiohydantoin has a fairly high degree of toxicity (421, 422). Diphenylthiohydantoin was reported to be inactive as an anticonvulsant (414). Both the 2-thio and 2,4-dithio derivatives of 5,5-dimethylhydantoin have been studied. Henze and Smith (317) found that 2,4-dithio-5,5-dimethylhydantoin showed no analgesic or anticonvulsant properties and only a slight hypnotic action in their

tests. This same compound, on the other hand, was found to show greater anticonvulsant activity, under other test conditions, than any of the three hydantoins obtained by replacing one or both of the sulfur atoms with oxygen (296).

The replacement of the *N*-3 hydrogen atom with a methyl group has been reported to reduce toxicity (448, 487), but at the same time to decrease the hypnotic action of 5-phenyl-5-alkylhydantoins (487) and to destroy the anticonvulsant activity of 5-phenyl-5-phenylethylhydantoin (309) and of 5,5-dimethyl-2,4-dithiohydantoin (297). However, 3-methyl-5-ethyl-5-phenylhydantoin, known as mesantoin, was recently reported by Aird (15) to be nearly as effective an anticonvulsant as dilantin, but with a very low toxicity.

Hydantoin derivatives have been prepared which combine the hydantoin nucleus with other chemical configurations known to be physiologically active, although none of these has achieved wide use in medicine. Among these are barbituric acid-hydantoin compounds (541, 543), 5-sulfanilamidohydantoins (516, 517, 542), *p*-phenolhydantoins (152), and hydantoins derived from cinchona alkaloids (447). The use of such hydantoins as 2-copper-mercapto-3-phenylhydantoin-5-acetic acid has been recommended for the treatment of tuberculosis and other infectious diseases (87).

B. Other uses of hydantoins

Hydantoins, thiohydantoins, and their substitution products have also found a number of uses other than as medicinal products. Among these applications are the use of water-soluble hydantoins in textile printing (579, 580), as catalysts for the polymerization of 1,3-butadiene hydrocarbons (586), and in the production of resins and plastics through interaction with formaldehyde (199). Indoxyl and indigo have been prepared from 1-phenylhydantoin through treatment of this hydantoin with a metallic oxide (187) or with alkali hydroxides or amides (215, 216); hydrolysis of 1-phenylhydantoin would form *N*-phenylglycine, which would then be converted into indoxyl and indigo. A propionic acid derivative of hydantoin was found to be an effective root-forming substance, nearly as effective as heteroauxin (3-indoleacetic acid), although the corresponding 2-thiohydantoin-propionic acid showed no effect (593).

Chlorinated hydantoins have been recommended for use as bleaching agents, antiseptics, and germicides (528, 529, 530); a germicidal rinse mixture, stable for long periods when stored as a solid even at high temperatures and humidities and retaining its germicidal properties in the presence of alkaline detergents, has been prepared from chlorinated hydantoins (497). Other uses for these chlorinated derivatives include their application as catalysts in the polymerization of methyl methacrylate (198), as stabilizers for vinyl chloride polymers (395), and for the peptization of diene hydrocarbon polymers prior to compounding (552). Dithiohydantoins have found use as corrosion inhibitors for metal pickling baths, as insecticides, and as resin intermediates (348).

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VIII. REFERENCES

(1) ABDERHALDEN, E.: Z. physiol. Chem. **251**, 164–70 (1938).
(2) ABDERHALDEN, E., AND HEYNS, K.: Z. physiol. Chem. **202**, 37–48 (1931).
(3) ALBERTI, C.: Atti X° congr. intern. chim. **3**, 21–6 (1939); Chem. Abstracts **34**, 1000 (1940).
(4) ALBERTI, C.: Gazz. chim. ital. **69**, 150–62 (1939); Chem. Abstracts **33**, 7283 (1939).
(5) ALLEN, B. B., AND HENZE, H. R.: J. Am. Chem. Soc. **60**, 1796–7 (1938).
(6) AMERICAN MEDICAL ASSOCIATION COMMITTEE ON PHARMACY AND CHEMISTRY: J. Am. Med. Assoc. **113**, 1734–5 (1939).
(7) ANDREASCH, R.: Ber. **12**, 1385–90 (1879).
(8) ANDREASCH, R.: Monatsh. **3**, 436–41 (1882).
(9) ANDREASCH, R.: Ber. **13**, 1423–7 (1880).
(10) ANDREASCH, R.: Monatsh. **16**, 789–97 (1895).
(11) ANDREASCH, R.: Monatsh. **23**, 803–15 (1902).
(12) ANDREWS, J. C., AND ANDREWS, K.: J. Biol. Chem. **102**, 253–62 (1933).
(13) ANGELI, A.: Atti accad. Lincei [5] **17, I**, 311–14 (1908).
(14) ANON.: Pharm. Zentralhalle **83**, 128–9 (1942); Chem. Abstracts **37**, 6408 (1943).
(15) ANON.: Chem. Eng. News **25**, 1888 (1947).
(16) ANSCHUTZ, R.: Ann. **254**, 258–61 (1889).
(17) ARMSTRONG, M. D., AND DU VIGNEAUD, V.: J. Biol. Chem. **168**, 373–7 (1947).
(18) ASAHINA, T.: Bull. Chem. Soc. Japan **4**, 202–9 (1929).
(19) ASAHINA, T.: Bull. Chem. Soc. Japan **5**, 354–65 (1930).
(20) ASCHAN, O.: Ber. **16**, 1544–5 (1883).
(21) ASCHAN, O.: Ber. **17**, 420–31 (1884).
(22) ASPELUND, H.: Finska Kemistsamfundets Medd. **49**, 49–63 (1940); Chem. Abstracts **35**, 2143 (1941).
(23) ASPELUND, H.: Acta Acad. Aboensis, Math. et Phys. **12**, No. 5, 33 pp. (1939).
(24) ASPELUND, H., AND HOLMBERG, G. A.: Finska Kemistsamfundets Festskrift-Juhlajulkaisu 1891–1941, **1944**, 250–6; Chem. Abstracts **41**, 5878 (1947).
(25) BAEYER, A.: Ann. **117**, 178–80 (1861).
(26) BAEYER, A.: Ann. **119**, 126–8 (1861).
(27) BAEYER, A.: Ann. **130**, 129–75 (1864).
(28) BAEYER, A.: Ann. **136**, 276–8 (1865).
(29) BAEYER, A.: Ber. **8**, 612–4 (1875).
(30) BAILEY, J. R.: Am. Chem. J. **28**, 386–403 (1902).
(31) BAILEY, J. R.: J. Am. Chem. Soc. **26**, 1006–26 (1904).
(32) BAILEY, J. R., AND MCPHERSON, A. T.: J. Am. Chem. Soc. **38**, 2523–7 (1916).
(33) BAILEY, J. R., AND PRITCHETT, R. H.: J. Am. Chem. Soc. **40**, 1230–5 (1918).
(34) BAILEY, J. R., AND RANDOLPH, C. P.: Ber. **41**, 2494–505 (1908).
(35) BAILEY, J. R., AND RANDOLPH, C. P.: Ber. **41**, 2505–8 (1908).
(36) BAILEY, J. R., AND READ, W. T.: J. Am. Chem. Soc. **37**, 1884–93 (1915).
(37) BAILEY, J. R., AND SNYDER, D. F.: J. Am. Chem. Soc. **37**, 935–42 (1915).
(38) BAILEY, J. R., AND SNYDER, D. F.: J. Am. Chem. Soc. **37**, 942–6 (1915).
(39) BARGER, G., AND EASSON, A. P. T.: J. Chem. Soc. **1938**, 2100–4.
(40) BAUDISCH, O., AND DAVIDSON, D.: J. Biol. Chem. **71**, 501–8 (1926).
(41) BAUDISCH, O., AND DAVIDSON, D.: J. Biol. Chem. **75**, 247–9 (1927).
(42) BAUMANN, E.: Ber. **7**, 237–9 (1874).
(43) BAUMANN, E., AND HOPPE-SEYLER, F.: Ber. **7**, 34–8 (1874).
(44) BAUMANN, L.: J. Biol. Chem. **21**, 563–6 (1915).
(45) BEHR, L. D., AND CLARKE, H. T.: J. Am. Chem. Soc. **54**, 1630–4 (1932).
(46) BEHREND, R., AND NIEMEYER, R.: Ann. **365**, 38–49 (1908).
(47) BERGMANN, M., AND DELIS, D.: Ann. **458**, 76–92 (1927).
(48) BERGMANN, M., AND MIEKELEY, A.: Ann. **458**, 40–75 (1927).

(49) BERGMANN, M., ZERVAS, L., RINKE, H., AND SCHLEICH, H.: Z. physiol. Chem. **224**, 26–33 (1934).
(50) BERGS, H.: German patent 566,094 (May 26, 1929); Chem. Abstracts **27**, 1001 (1933).
(51) BILTZ, H.: Ber. **40**, 4806–16 (1907).
(52) BILTZ, H.: Ber. **41**, 167–73 (1908).
(53) BILTZ, H.: Ber. **41**, 1379–93 (1908).
(54) BILTZ, H.: Ber. **42**, 1792–1800 (1909).
(55) BILTZ, H.: Ber. **43**, 1589–1600 (1910).
(56) BILTZ, H.: Ber. **43**, 1600–18 (1910).
(57) BILTZ, H.: Ber. **43**, 1618–32 (1910).
(58) BILTZ, H.: Ber. **46**, 3407–10 (1913).
(59) BILTZ, H.: Ann. **423**, 119–323 (1921).
(60) BILTZ, H., AND BEHRENS, O.: Ber. **43**, 1984–6 (1910).
(61) BILTZ, H., AND BERGIUS, M.: Ann. **414**, 54–67 (1918).
(62) BILTZ, H., AND HEIDRICH, D.: Ber. **54**, 1829–33 (1921).
(63) BILTZ, H., AND HEYN, M.: Ber. **45**, 1666–77 (1912).
(64) BILTZ, H., AND HEYN, M.: Ann. **413**, 7–60 (1917).
(65) BILTZ, H., HEYN, M., AND BERGIUS, M.: Ann. **413**, 68–77 (1917).
(66) BILTZ, H., HEYN, M., AND BERGIUS, M.: Ann. **413**, 77–87 (1917).
(67) BILTZ, H., AND KLEIN, H.: Ber. **58**, 2740–7 (1925).
(68) BILTZ, H., AND KOBEL, M.: Ber. **54**, 1802–28 (1921).
(69) BILTZ, H., AND KREBS, P.: Ber. **44**, 282–305 (1911).
(70) BILTZ, H., AND KRZIKALLA, H.: Ann. **457**, 131–89 (1927).
(71) BILTZ, H., AND LACHMANN, F.: J. prakt. Chem. **136**, 217–31 (1933).
(72) BILTZ, H., AND LEMBERG, R.: Ann. **432**, 137–76 (1923).
(73) BILTZ, H., AND LOEWE, L., J. prakt. Chem. **141**, 284–98 (1934).
(74) BILTZ, H., AND MAX, F.: Ann. **414**, 68–78 (1918).
(75) BILTZ, H., AND MAX, F.: Ann. **414**, 79–84 (1918).
(76) BILTZ, H., AND MAX, F.: Ann. **414**, 85–98 (1918).
(77) BILTZ, H., AND MAX, F.: Ber. **54**, 2451–76 (1921).
(78) BILTZ, H., AND ROBL, R.: Ber. **54**, 2441–8 (1921).
(79) BILTZ, H., AND SEYDEL, K.: Ber. **46**, 138–42 (1913).
(80) BILTZ, H., AND SLOTTA, K.: J. prakt. Chem. **113**, 233–67 (1926).
(81) BILTZ, H., AND TOPP, E.: Ber. **44**, 1511–23 (1911).
(82) BILTZ, H., AND TOPP, E.: Ber. **44**, 1524–32 (1911).
(83) BISCHOFF, C. A., AND HAUSDÖRFER, A.: Ber. **25**, 2270–80 (1892).
(84) BLAIR, D.: J. Mental Sci. **86**, 888–927 (1940).
(85) BLENDERMANN, H.: Z. physiol. Chem. **6**, 234–62 (1882).
(86) BLOCH, K., AND CLARKE, H. T.: J. Biol. Chem. **125**, 275–87 (1938).
(87) BOCKMÜHL, W., AND PERSCH, W.: U. S. patent 2,323,445 (July 6, 1944); Chem. Abstracts **38**, 220 (1944).
(88) BOLLER, W.: Schweiz. med. Wochschr. **73**, 699–707 (1943); Chem. Abstracts **38**, 5007 (1944).
(89) BOON, W. R., AND ROBSON, W.: Biochem. J. **29**, 2573–5 (1935).
(90) BOTVINICK, M. M., AND GAVRILOV, N. I.: J. prakt. Chem. **148**, 170–90 (1937).
(91) BOUGAULT, J., AND CHABRIER, P.: Compt. rend. **213**, 400–2 (1941).
(92) BOVARNICK, M., AND CLARKE, H. T.: J. Am. Chem. Soc. **60**, 2426–30 (1938).
(93) BOYD, W. J.: Biochem. J. **27**, 1838–48 (1933).
(94) BOYD, W. J., AND ROBSON, W.: Biochem. J. **29**, 542–5 (1935).
(95) BOYD, W. J., AND ROBSON, W.: Biochem. J. **29**, 546–54 (1935).
(96) BOYD, W. J., AND ROBSON, W.: Biochem. J. **29**, 2256–8 (1935).
(97) BRAUN, J. VON: Ber. **42**, 839–46 (1909).
(98) BRAUTLECHT, C.: J. Biol. Chem. **10**, 139–46 (1911).
(99) BRENZINGER, K.: Z. physiol. Chem. **16**, 552–88 (1892).

(100) BRITTON, E. C., AND LIVAK, J. E.: U. S. patent 2,435,125 (January 27, 1948); Chem. Abstracts **42**, 4613 (1948).
(101) BUCHERER, H. T., AND BARSCH, H.: J. prakt. Chem. **140**, 151–71 (1934).
(102) BUCHERER, H. T., AND BRANDT, W.: J. prakt. Chem. **140**, 129–50 (1934).
(103) BUCHERER, H. T., AND FISHBECK, H.: J. prakt. Chem. **140**, 69–89 (1934).
(104) BUCHERER, H. T., AND LIEB, V. A.: J. prakt. Chem. **141**, 5–43 (1934).
(105) BUCHERER, H. T., AND STEINER, W.: J. prakt. Chem. **140**, 291–316 (1934).
(106) BUSINGER, A.: Jubilee Vol. Emil Barel **1946**, 137–48; Chem. Abstracts **41**, 3790 (1947).
(107) BUSINGER, A.: U. S. patent 2,436,851 (March 2, 1948); Chem. Abstracts **42**, 4612 (1948).
(108) BYWATER, W. G.: U. S. patent 2,242,775 (May 20, 1941); Chem. Abstracts **35**, 5520 (1941).
(109) CAHEN, R. L.: J. Pharmacol. **88**, 343–52 (1946).
(110) CARR, E. P., AND DOBBROW, M. A.: J. Am. Chem. Soc. **47**, 2961–5 (1925).
(111) CARRINGTON, H. C.: British patent 512,629 (September 21, 1939); Chem. Abstracts **35**, 758 (1941).
(112) CARRINGTON, H. C.: J. Chem. Soc. **1947**, 681-3.
(113) CARRINGTON, H. C.: J. Chem. Soc. **1947**, 684–6.
(114) CATCH, J. R., COOK, A. H., GRAHAM, A. R., AND HEILBRON, I.: J. Chem. Soc. **1947**, 1609–13.
(115) CATTELAIN, E., AND CHABRIER, P.: Compt. rend. **218**, 623–4 (1944).
(116) CATTELAIN, E., AND CHABRIER, P.: Bull. soc. chim. France **1947**, 639–42.
(117) CAVALIERI, L. F., AND BROWN, G. B.: J. Am. Chem. Soc. **70**, 1242–3 (1948).
(118) CERCHEZ, V.: Thesis; "Hydantoin-acetic acids," Lyons, 1929.
(119) CERCHEZ, V.: Bull. soc. chim. France [4] **49**, 52–4 (1931).
(120) CHABRIER, P.: Ann. chim. **17**, 353–70 (1942).
(121) CHABRIER, P., AND TCHOUBAR, B.: Compt. rend. **220**, 284–6 (1945).
(122) CHABRIER, P., TCHOUBAR, B., AND LE TELLIER-DUPRÉ, S.: Bull. soc. chim. France **1946**, 332–40.
(123) CHEMISCHE FABRIK VON HEYDEN A.-G.: German patent 309,508 (January 23, 1919); Chem. Zentr. **1919, II**, 262.
(124) CHEMISCHE FABRIK VON HEYDEN A.-G.: German patent 310,426 (January 23, 1919); Chem. Zentr. **1919, II**, 262.
(125) CHEMISCHE FABRIK VON HEYDEN A.-G.: German patent 310,427 (January 30, 1919); Chem. Zentr. **1919, II**, 423–4.
(126) CHEMISCHE FABRIK VON HEYDEN A.-G.: German patent 335,993 (April 20, 1921); Chem. Abstracts **17**, 1802 (1923).
(127) CHEMISCHE FABRIK VON HEYDEN A.-G.: German patent 335,994 (April 22, 1921); Chem. Abstracts **17**, 1801 (1923).
(128) CHEMISCHE FABRIK VON HEYDEN A.-G.: German patent 360,688 (June 10, 1922); Chem. Abstracts **18**, 842 (1924).
(129) CHEMISCHE FABRIK VON HEYDEN A.-G.: German patent 602,218 (September 3, 1934); Chem. Abstracts **29**, 1105 (1935).
(130) CHEMISCHE FABRIK VORM. SANDOZ: Swiss patent 166,004 (February 16, 1934); Chem. Abstracts **28**, 2850 (1934).
(131) CHEMISCHE FABRIK VORM. SANDOZ: Swiss patent 168,947-8 (July 16, 1934); Chem. Abstracts **29**, 554 (1935).
(132) CHEMISCHE FABRIK VORM. SANDOZ: German patent 611,057 (March 21, 1935); Chem. Abstracts **29**, 4025 (1935).
(133) CHEMISCHE FABRIK VORM. SANDOZ: British patent 430,255 (June 17, 1935); Chem. Abstracts **29**, 7343 (1935).
(134) CHEMISCHE FABRIK VORM. SANDOZ: Swiss patent 176,827 (July 16, 1935); Chem. Abstracts **30**, 248 (1936).
(135) CHEMISCHE FABRIK VORM. SANDOZ: Swiss patent 177,411 (September 2, 1935); Chem. Abstracts **30**, 3592 (1936).

(136) CHEMISCHE FABRIK VORM. SANDOZ: Swiss patent 179,255 (November 15, 1935); Chem. Abstracts **30**, 3592 (1936).
(137) CHEMISCHE FABRIK VORM. SANDOZ: Swiss patent 179,690–1 (December 2, 1935); Chem. Abstracts **30**, 3592 (1936).
(138) CHEMISCHE FABRIK VORM. SANDOZ: Swiss patent 181,175–6 (February 17, 1936); Chem. Abstracts **30**, 8530 (1936).
(139) CHEMISCHE FABRIK VORM. SANDOZ: German patent 634,198 (August 20, 1936); Chem. Abstracts **30**, 8532 (1936).
(140) CHEMISCHE FABRIK VORM. SANDOZ: French patent 807,125 (January 5, 1937); Chem. Abstracts **31**, 5515 (1937).
(141) CHEMISCHE FABRIK VORM. SANDOZ: Swiss patent 188,239 (March 1, 1937); Chem. Abstracts **31**, 5110 (1937).
(142) CHEMISCHE FABRIK VORM. SANDOZ: Swiss patent 188,442 (March 16, 1937); Chem. Abstracts **31**, 6822 (1937).
(143) CHEYMOL, J.: J. pharm. chim. [9] **2**, 305–9 (1942); Chem. Zentr. **1942, II**, 2496.
(144) CHU, W. C., AND DRIVER, R. L.: Proc. Soc. Exptl. Biol. Med. **64**, 245–8 (1947).
(145) CIAMICIAN, G., AND SILBER, P.: Ber. **38**, 1671–5 (1905).
(146) CIAMICIAN, G., AND SILBER, P.: Ber. **47**, 1806–14 (1914).
(147) CLARKE, C. H., AND FRANCIS, F.: J. Chem. Soc. **99**, 319–25 (1911).
(148) COCKER, W.: J. Chem. Soc. **1937**, 1693–5.
(149) COCKER, W.: J. Chem. Soc. **1940**, 1489–91.
(150) COCKER, W., AND HARRIS, J. O.: J. Chem. Soc. **1940**, 1290–5.
(151) COCKER, W., AND LAPWORTH, A.: J. Chem. Soc. **1931**, 1391–1403.
(152) COGHILL, R. D.: J. Am. Chem. Soc. **47**, 216–21 (1925).
(153) COGHILL, R. D., AND JOHNSON, T. B.: J. Am. Chem. Soc. **47**, 184–93 (1925).
(154) COHN, E. J., MCMEEKIN, T. L., GREENSTEIN, J. P., AND COHN, J. H.: J. Am. Chem. Soc. **58**, 2365–70 (1936).
(155) COLLIP, J. B., AND SANDIN, R.: Trans. Roy Soc. Can. **22**, V, 185–6 (1928).
(156) CONNER, W. P., CLARKE, R. P., AND SMYTH, C. P.: J. Am. Chem. Soc. **64**, 1379–87 (1942).
(157) COOK, A. H., HEILBRON, I. M., AND LEVY, A. L.: J. Chem. Soc. **1947**, 1598–1609.
(158) COOK, A. H., HEILBRON, I. M., AND LEVY, A. L.: J. Chem. Soc. **1948**, 201–6.
(159) COOK, A. H., HEILBRON, I. M., AND STERN, E. S.: J. Chem. Soc. **1948**, 2031–3.
(160) CORWIN, A. H., AND DAMEREL, C. I.: J. Am. Chem. Soc. **65**, 1974–84 (1943).
(161) CRAIG, W. C., AND HENZE, H. R.: J. Org. Chem. **10**, 10–15 (1945).
(162) CRAIG, W. C., AND HENZE, H. R.: J. Org. Chem. **10**, 16–20 (1945).
(163) CREECH, H. J.: J. Am. Chem. Soc. **63**, 576–8 (1941).
(164) CSONKA, F. A., AND NICOLET, B. H.: J. Biol. Chem. **99**, 213–6 (1932).
(165) CURTIUS, T., SIEBER, W., NADENHEIM, F., HAMBSCH, O., AND RITTER, W.: J. prakt. Chem. **125**, 152–210 (1930).
(166) DAINS, F. B., THOMPSON, R., AND ASENDORF, W. F.: J. Am. Chem. Soc. **44**, 2310–5 (1922).
(167) DAKIN, H. D.: J. Biol. Chem. **6**, 235–43 (1909).
(168) DAKIN, H. D.: Am. Chem. J. **44**, 48–60 (1910).
(169) DAKIN, H. D.: J. Biol. Chem. **8**, 25–39 (1910).
(170) DAKIN, H. D.: J. Chem. Soc. **107**, 434–9 (1915).
(171) DAKIN, H. D.: Biochem. J. **13**, 398–429 (1919).
(172) DAKIN, H. D.: J. Biol. Chem. **146**, 237–40 (1942).
(173) DAKIN, H. D., AND DUDLEY, H. W.: J. Biol. Chem. **17**, 29–36 (1914).
(174) DALGLIESH, C. E., AND MANN, F. G.: J. Chem. Soc. **1947**, 559–60.
(175) DAMODARAN, M., AND RAMASWAMY, R.: Biochem. J. **31**, 2149–52 (1937).
(176) DAVIDSON, D.: J. Am. Chem. Soc. **47**, 255–9 (1925).
(177) DAVIDSON, D., AND JOHNSON, T. B.: J. Am. Chem. Soc. **47**, 561–7 (1925).
(178) DAVIS, T. L., AND BLANCHARD, K. C.: J. Am. Chem. Soc. **51**, 1790–1801 (1929).
(179) DAY, A. R., AND KELLY, C. F.: J. Org. Chem. **4**, 101–2 (1939).

(180) DECK, J. F., AND DAINS, F. B.: J. Am. Chem. Soc. **55**, 4986–91 (1933).
(181) DELÉPINE, M.: Bull. soc. chim. [3] **29**, 1190–6, 1198–1202 (1903).
(182) DEULOFEU, V.: Z. physiol. Chem. **204**, 214–18 (1932).
(183) DEULOFEU, V.: Ber. **69**, 2456–9 (1936).
(184) DEULOFEU, V., AND MENDIVE, J.: Z. physiol. Chem. **211**, 1–4 (1932).
(185) DEULOFEU, V., AND MENDIVELZUA, G.: Z. physiol. Chem. **219**, 233–9 (1933).
(186) DEULOFEU, V., AND REPETTO, O.: Anales soc. españ. fís. y quím. **32**, 159–64 (1934); Chem. Abstracts **28**, 3723 (1934).
(187) DEUTSCHE GOLD- UND SILBER-SCHEIDEANSTALT VORM. RÖSSLER: German patent **142**, 700 (July 8, 1903); Chem. Zentr. **1903, II**, 271.
(188) DEVOTO, G., COLA, G., AND ZOCCOLINI, G.: Gazz. chim. ital. **63**, 50–8 (1933); Chem. Abstracts **27**, 3449 (1933).
(189) DIELS, O., AND HEINTZEL, H.: Ber. **38**, 297–305 (1905).
(190) DIXON, A. E.: J. Chem. Soc. **71**, 617–41 (1897).
(191) DOUGLASS, I. B., AND DAINS, F. B.: J. Am. Chem. Soc. **56**, 719–21 (1934).
(192) DRAKE, M. E., GRUBER, C. M., AND HAURY, V. G.: J. Pharmacol. **71**, 268–72 (1941).
(193) DRAKE, M. E., GRUBER, C. M., HAURY, V. G., AND HART, E. R.: J. Pharmacol. **72**, 383–5 (1941).
(194) DUBSKY, J. V.: Mikrochemie **28**, 145–72 (1940).
(195) DUBSKY, J. V., AND CERNAK, V.: Pubs. faculté sci. univ. Masaryk **269**, 9–20 (1939); Chem. Abstracts **33**, 7278 (1939).
(196) DUBKSY, J. V., SINDELAR, V., AND CERNAK, V.: Mikrochemie **25**, 124–42 (1938).
(197) DUBSKY, J. V., AND VRBOVA, J.: Chem. Obzor. **16**, 115–7 (1941); Chem. Zentr. **1942, I**, 2804.
(198) DU PONT DE NEMOURS, E. I., AND COMPANY: British patent 582,719 (November **26**, 1946); Chem. Abstracts **41**, 6078 (1947).
(199) DU PONT DE NEMOURS, E. I., AND COMPANY, AND WALKER, J. F.: British patent **564**, 424 (September 27, 1944); Chem. Abstracts **40**, 3300 (1946).
(200) DUTCHER, J. D., JOHNSON, J. R., AND BRUCE, W. F.: J. Am. Chem. Soc. **67**, 1736–45 (1945).
(201) DUTT, S., AND AGARWAL, B. M. S.: Proc. Indian Acad. Sci. **11A**, 96–105 (1940).
(202) DU VIGNEAUD, V., MCKENNIS, H., SIMMONDS, S., DITTMER, K., AND BROWN, G. B.: J. Biol. Chem. **159**, 385–94 (1945).
(203) DUVILLIER, M. E.: Bull. soc. chim. [3] **13**, 487–90 (1895).
(204) EBERLY, F. A., AND DAINS, F. B.: J. Am. Chem. Soc. **58**, 2544–7 (1936).
(205) EHRLICH, A.: Ber. **16**, 742–3 (1883).
(206) ELKS, J., ELLIOTT, D. F., AND HEMS, B. A.: J. Chem. Soc. **1944**, 624–5.
(207) ELLINGER, A., AND MATSUOKA, Z.: Z. physiol. Chem. **89**, 441 (1914).
(208) ELLIS, L. S. E., AND CHEMISCHE FABRIK VORM. SANDOZ: British patent 430,282 (June 17, 1935); Chem. Abstracts **29**, 7344 (1935).
(209) ELLIS, L. S. E., AND CHEMISCHE FABRIK VORM. SANDOZ: British patent 430,283 (June 17, 1935); Chem. Abstracts **29**, 7344 (1935).
(210) EMERSON, G. A.: Proc. Soc. Exptl. Biol. Med. **54**, 252–4 (19)43.
(211) EMMETT, A. D., HARTZLER, E. R., AND BROWN, R. A.: J. Pharmacol. **78**, 215–21 (1943).
(212) ERLENMEYER, H., AND KLEIBER, A.: Helv. Chim. Acta **22**, 851–2 (1939).
(213) ERRERA, G.: Gazz. chim. ital. **26, I**, 197–211 (1896); Brit. Chem. Abstracts **70, I**, 528 (1896).
(214) EVANS, W. C., AND WALKER, N.: J. Chem. Soc. **1947**, 1571–3.
(215) FARBWERKE VORM. MEISTER, LUCIUS AND BRÜNING: German patent 132,477 (June 14, 1902); Chem. Zentr. **1902, II**, 173.
(216) FARBWERKE VORM. MEISTER, LUCIUS AND BRÜNING: German patent 163,039 (September 12, 1905); Chem. Zentr. **1905, II**, 1140.
(217) FARBWERKE VORM. MEISTER, LUCIUS AND BRÜNING: Swiss patent 72,561 (September 16, 1916); Chem. Abstracts **11**, 186 (1917).

(218) FARBWERKE VORM. MEISTER, LUCIUS AND BRÜNING: Swiss patent 74,094 (January 16, 1917); Chem. Abstracts **11**, 1884 (1917).
(219) FARBWERKE VORM. MEISTER, LUCIUS AND BRÜNING: Swiss patent 74,189 (February 1, 1917); Chem. Abstracts **11**, 1884 (1917).
(220) FARBWERKE VORM. MEISTER, LUCIUS AND BRÜNING: Swiss patent 74,190 (February 1, 1917); Chem. Abstracts **11**, 1885 (1917).
(221) FIESER, L. F., AND CREECH, H. J.: J. Am. Chem. Soc. **61**, 3502–6 (1939).
(222) FINKELMAN, I., AND ARIEFF, A. J.: J. Am. Med. Assoc. **118**, 1209–12 (1942).
(223) FISCHER, E.: Ann. **215**, 253–320 (1882).
(224) FISCHER, E.: Ber. **33**, 2370–83 (1900).
(225) FISCHER, E.: Ber. **34**, 433–54 (1901).
(226) FISCHER, E.: Z. physiol. Chem. **33**, 151–76 (1901).
(227) FISCHER, E., AND ACH, F.: Ber. **32**, 2721–49 (1899).
(228) FISHCER, E., AND LEUCHS, H.: Ber. **35**, 3787–3805 (1902).
(229) FISCHER, E., AND MOUNEYRAT, A.: Ber. **33**, 2383–93 (1900).
(230) FISCHER, E., AND OTTO, E.: Ber. **36**, 2106–16 (1903).
(231) FISHER, H. J., EKELEY, J. B., AND RONZIO, A. R.: J. Am. Chem. Soc. **64**, 1434–6 (1942).
(232) FOSSE, R., HAGÈNE, P., AND DUBOIS, R.: Compt. rend. **178**, 578–81 (1924).
(233) FRANCHIMONT, A. P. N., AND KLOBBIE, E. A.: Rec. trav. chim. **7**, 12–24 (1888).
(234) FRANCHIMONT, A. P. N., AND KLOBBIE, E. A.: Rec trav. chim. **7**, 236–57 (1888).
(235) FRANCHIMONT, A. P. N., AND KLOBBIE, E. A.: Rec. trav. chim. **8**, 283–306 (1889).
(236) FRANCHIMONT, A. P. N., AND VAN ERP, H.: Rec. trav. chim. **15**, 165–73 (1896).
(237) FRANKLAND, E. P., AND SMITH, H. E.: J. Chem. Soc. **103**, 998–1004 (1913).
(238) FRERICHS, G., AND BECKURTS, H.: Arch. Pharm. **237**, 331–46 (1899).
(239) FRERICHS, G., AND BREUSTEDT, G.: J. prakt. Chem. [2] **66**, 231–61 (1902).
(240) FRERICHS, G., AND HOLLMANN, M.: Arch. Pharm. **243**, 684–710 (1905).
(241) FREUND, W.: Deut. med. Wochschr. **45**, 1388–9 (1919); Chem. Abstracts **14**, 1153 (1920).
(242) FREYTAG, B.: J. prakt. Chem. [2] **20**, 380–2 (1879).
(243) FRIEDMAN, E.: Beitr. chem. Physiol. Path. **11**, 158–76 (1908).
(244) GABRIEL, S.: Ann. **348**, 50–90 (1906).
(245) GABRIEL, S.: Ann. **350**, 118–34 (1906).
(246) GAEBLER, O. H.: J. Biol. Chem. **69**, 613–24 (1926).
(247) GARRIDO, J.: Anales fís. y quím. (Madrid) **43**, 1195–1202 (1947); Chem. Abstracts **42**, 3287 (1948).
(248) GATEWOOD, E. S.: J. Am. Chem. Soc. **45**, 3056–64 (1923).
(249) GATEWOOD, E. S.: J. Am. Chem. Soc. **47**, 2175–81 (1925).
(250) GAUDRY, R.: Can. J. Research **23B**, 234–7 (1945).
(251) GAUDRY, R.: Can. J. Research **26B**, 387–92 (1948).
(252) GAUDRY, R.: Can. J. Research **26B**, 773–6 (1948).
(253) GAUDRY, R., AND NADEAU, G.: Can. J. Research **26B**, 226–9 (1948).
(254) GHOSH, T. N.: J. Indian Chem. Soc. **11**, 23–32 (1934).
(255) GHOSH, T. N.: J. Indian Chem. Soc. **14**, 113–15 (1937).
(256) GORDON, A. S., GOLDSMITH, E. D., AND CHARIPPER, H. A.: Proc. Soc. Exptl. Biol. Med. **56**, 202–3 (1944).
(257) GORDON, W. G., AND JACKSON, R. W.: J. Biol. Chem. **110**, 151 (1935).
(258) GORTNER, R. A., AND HOFFMAN, W. F.: J. Biol. Chem. **72**, 433–48 (1927).
(259) GORVIN, J. H.: Nature **161**, 208 (1948).
(260) GRANACHER, C., AND LANDOLT, H.: Helv. Chim. Acta **10**, 799–815 (1927).
(261) GRANACHER, C., AND WOLF, G.: Helv. Chim. Acta **11**, 172–9 (1928).
(262) GRESHAM, W. F., AND SCHWEITZER, C. E.: U. S. patent 2,402,134 (June 18, 1946); Chem. Abstracts **40**, 6095 (1946).
(263) GRIESS, P.: Ber. **2**, 106–7 (1869).
(264) GRIMAUX, E.: Compt. rend. **81**, 325–7 (1875).
(265) GRIMAUX, E.: Ber. **8**, 545 (1875).

(266) GRIMAUX, E.: Bull. soc. chim. [2] **24**, 337–55 (1875).
(267) GRIMAUX, E.: Ann. chim. phys. [5] **11**, 402 (1877).
(268) GRUBER, C. M., HAURY, V. G., AND DRAKE, M. E.: J. Pharmacol. **68**, 433–6 (1940).
(269) GUARESCHI, J.: Ber. **8**, 1197–1201 (1875).
(270) GUARESCHI, J.: Gazz. chim. ital. **6**, 370 (1876); Chem. Zentr. **1876**, 771.
(271) GUARESCHI, J.: Ber. **9**, 1435 (1876).
(272) GUARESCHI, J.: Gior. accad. med. **1891**; Chem. Zentr. **1892**, I, 140.
(273) GULEWITSCH, W.: Z. physiol. Chem. **73**, 434–46 (1911).
(274) HAHN, D. A., AND BURT, C. P.: J. Am. Chem. Soc. **39**, 2468–72 (1917).
(275) HAHN, D. A., AND DYER, E.: J. Am. Chem. Soc. **52**, 2494–2504 (1930).
(276) HAHN, D. A., AND DYER, E.: J. Am. Chem. Soc. **52**, 2505–12 (1930).
(277) HAHN, D. A., AND ENDICOTT, M. M.: J. Am. Chem. Soc. **59**, 2740–1 (1937).
(278) HAHN, D. A., AND ENDICOTT, M. M.: J. Am. Chem. Soc. **60**, 1040–5 (1938).
(279) HAHN, D. A., AND EVANS, J.: J. Am. Chem. Soc. **49**, 2877–83 (1927).
(280) HAHN, D. A., AND EVANS, J.: J. Am. Chem. Soc. **50**, 806–18 (1928).
(281) HAHN, D. A., AND GILMAN, E.: J. Am. Chem. Soc. **47**, 2941–53 (1925).
(282) HAHN, D. A., AND GILMAN, E.: J. Am. Chem. Soc. **47**, 2953–61 (1925).
(283) HAHN, D. A., AND LITZINGER, A.: J. Am. Chem. Soc. **54**, 4663–7 (1932).
(284) HAHN, D. A., MCLEAN, M. J., AND ENDICOTT, M. M.: J. Am. Chem. Soc. **62**, 1087–91 (1940).
(285) HAHN, D. A., MCLEAN, M. J. AND MURPHY, H. T.: J. Am. Chem. Soc. **60**, 1927–9 (1938).
(286) HAHN, D. A., AND RENFREW, A. G.: J. Am. Chem. Soc. **47**, 147–63 (1925).
(287) HAHN, D. A., AND SEIKEL, M. K.: J. Am. Chem. Soc. **58**, 647–9 (1936).
(288) HARING, K. M., AND JOHNSON, T. B.: J. Am. Chem. Soc. **55**, 395–402 (1933).
(289) HARRIES, C.: Ann. **361**, 69–72 (1908).
(290) HARRIES, C., AND WEISS, M.: Ber. **33**, 3418–20 (1900).
(291) HARRIES, C., AND WEISS, M.: Ann. **327**, 355–84 (1903).
(292) HARVEY, D. G., AND ROBSON, W.: J. Chem. Soc. **1938**, 97–101.
(293) HARVILL, E. K., AND HERBST, R. M.: J. Org. Chem. **9**, 21–30 (1944).
(294) HATT, H. H., PILGRIM, A., AND HURRAN, W. J.: J. Chem. Soc. **1936**, 93–6.
(295) HAURY, V. G., AND DRAKE, M. E.: J. Pharmacol. **68**, 36–40 (1940).
(296) HAZARD, R., CHEYMOL, J., CHABRIER, P., AND SMARZEWSKA, K.: Compt. rend. **226**, 1850–2 (1948).
(297) HAZARD, R., CHEYMOL, J., CHABRIER, P., AND SMARZEWSKA, K.: Compt. rend. **226**, 2018–19 (1948).
(298) HEILPERN, J.: Monatsh. **17**, 229–44 (1896).
(299) HEINTZ, W.: Ann. **133**, 65–74 (1865).
(300) HEINTZ, W.: Ann. **169**, 120–30 (1873).
(301) HENTSCHEL, W.: Ber. **31**, 508–10 (1898).
(302) HENZE, H. R.: U. S. patent 2,290,281 (July 21, 1942); Chem. Abstracts **37**, 502 (1943).
(303) HENZE, H. R.: U. S. patent 2,327,890 (August 24, 1943); Chem. Abstracts **38**, 837 (1944).
(304) HENZE, H. R.: U. S. patents 2,409,754, 2,409,755, 2,409,756 (October 22, 1946); Chem. Abstracts **41**, 1250 (1947).
(305) HENZE, H. R., AND CRAIG, W. C.: J. Org. Chem. **10**, 2–9 (1945).
(306) HENZE, H. R., AND HOLDER, C. B.: J. Am. Chem. Soc. **63**, 1943–5 (1941).
(307) HENZE, H. R., AND HOLDER, C. B.: J. Am. Chem. Soc. **66**, 1545–7 (1944).
(308) HENZE, H. R., AND HUMPHREYS, D. D.: J. Am. Chem. Soc. **64**, 2881 (1942).
(309) HENZE, H. R., AND LONG, L. M.: J. Am. Chem. Soc. **63**, 1936–8 (1941).
(310) HENZE, H. R., AND LONG, L. M.: J. Am. Chem. Soc. **63**, 1941–3 (1941).
(311) HENZE, H. R., LONG, L. M., SPEER, R. J., AND THOMPSON, T. R.: J. Am. Chem. Soc. **65**, 323–5 (1943).
(312) HENZE, H. R., AND MCKEE, R. L.: J. Am. Chem. Soc. **64**, 1672–4 (1942).
(313) HENZE, H. R., AND MAGEE, J. W.: J. Am. Chem. Soc. **62**, 912–3 (1940).

(314) HENZE, H. R., MELTON, J. W., AND FORMAN, E. O.: J. Am. Chem. Soc. **70**, 2438–9 (1948).
(315) HENZE, H. R., AND NUNN, L. G.: J. Org. Chem. **12**, 543–6 (1947).
(316) HENZE, H. R., AND SHOWN, J. H.: J. Am. Chem. Soc. **69**, 1662–6 (1947).
(317) HENZE, H. R., AND SMITH, P. E.: J. Am. Chem. Soc. **65**, 1090–2 (1943).
(318) HENZE, H. R., AND SPEER, R. J.: J. Am. Chem. Soc. **64**, 522–3 (1942); see also American Documentation Institute, Document No. 1603.
(319) HENZE, H. R., THOMPSON, T. R., AND SPEER, R. J.: J. Org. Chem. **8**, 17–28 (1943).
(320) HENZE, H. R., WHITNEY, W. B., AND EPPRIGHT, M. A.: J. Am. Chem. Soc. **62**, 565–8 (1940).
(321) HENZE, H. R., WILSON, R. C., AND TOWNLEY, R. W.: J. Am. Chem. Soc. **65**, 963–5 (1943).
(322) HEPNER, B., AND FRENKENBERG, S.: J. prakt. Chem. **134**, 249–56 (1932).
(323) HERBST, R. M., AND JOHNSON, T. B.: J. Am. Chem. Soc. **52**, 3676–80 (1930).
(324) HERBST, R. M., AND JOHNSON, T. B.: J. Am. Chem. Soc. **54**, 2463–90 (1932).
(325) HERBST, R. M., AND RITTENBERG, D.: J. Org. Chem. **8**, 380–9 (1943).
(326) HERMANNS, L.: U. S. patent 1,285,703 (November 26, 1918); Chem. Abstracts **13**, 248 (1919).
(327) HERZ, W., AND DITTMER, K.: J. Am. Chem. Soc. **70**, 503 (1948).
(328) HERZOG, G.: Ann. **136**, 278–87 (1865).
(329) HESS, W. C.: J. Am. Chem. Soc. **56**, 1421 (1934).
(330) HEYMANN, H., AND FIESER, L. F.: J. Am. Chem. Soc. **67**, 1979–86 (1945).
(331) HILL, A. J., AND HENZE, H. R.: J. Am. Chem. Soc. **46**, 2806–10 (1924).
(332) HILL, A. J., AND KELSEY, E. B.: J. Am. Chem. Soc. **44**, 2357–69 (1922).
(333) HILL, E. M., AND ROBSON, W.: Biochem. J. **30**, 248–51 (1936).
(334) HIRAI, K.: Biochem. Z. **177**, 449–52 (1926).
(335) HOFF, E. C., AND YAHN, C.: Am. J. Physiol. **141**, 7–16 (1944).
(336) HOPKINS, S. J., AND WORMALL, A.: Biochem. J. **28**, 229–36 (1934).
(337) HOPPE-SEYLER, F. A.: Z. physiol. Chem. **214**, 267–70 (1933).
(338) HORBACZEWSKI, J.: Monatsh. **8**, 584–93 (1887).
(339) HUANG, Y., LIN, K., AND LI, L.: J. Chinese Chem. Soc. **15**, 31–7 (1947); Chem. Abstracts **42**, 523 (1948).
(340) HUANG, Y., LIN, K., AND LI, L.: J. Chinese Chem. Soc. **15**, 46–54 (1947); Chem. Abstracts **42**, 4941 (1948).
(341) HUGOUNENQ, M., AND MOREL, A.: Compt. rend. **140**, 150–1 (1905).
(342) HUPPERT, H.: Ber. **6**, 1278–80 (1873).
(343) INGOLD, C. K., SAKO, S., AND THORPE, J. F.: J. Chem. Soc. **121**, 1177–98 (1922).
(344) ISEKI, T.: Z. physiol. Chem. **216**, 127–30 (1933).
(345) IWAO, Z., KATUMURA, T., AND KOTAKE, M.: J. Chem. Soc. Japan **60**, 454–6 (1939).
(346) JACKMAN, M., KLENK, M., FISHBURN, B., TULLAR, B. F., AND ARCHER, S.: J. Am. Chem. Soc. **70**, 2884–6 (1948).
(347) JACOB, C.: Deut. med. Wochschr. **45**, 1331–2 (1919); Chem. Abstracts **14**, 1152 (1920).
(348) JACOBSON, R. A.: U. S. patent 2,143,816 (January 10, 1939); Chem. Abstracts **33**, 2882 (1939).
(349) JACOBSON, R. A.: J. Am. Chem. Soc. **67**, 1996–8 (1945).
(350) JAFFE, M.: Z. physiol. Chem. **7**, 306–14 (1883).
(351) JANSEN, M. P. J. M.: Rec. trav. chim. **50**, 291–312 (1931).
(352) JERZMANOWSKA-SIENKIEWICZOWA, Z.: Roczniki Chem. **15**, 202–8 (1935).
(353) JERZMANOWSKA-SIENKIEWICZOWA, Z.: Roczniki Chem. **15**, 510–15 (1935).
(354) JERZMANOWSKA-SIENKIEWICZOWA, Z.: Roczniki Chem. **16**, 172–9 (1936).
(355) JOHNSON, T. B.: J. Biol. Chem. **11**, 97–101 (1912).
(356) JOHNSON, T. B.: Am. Chem. J. **49**, 68–9 (1913).
(357) JOHNSON, T. B.: J. Am. Chem. Soc. **35**, 780–4 (1913).
(358) JOHNSON, T. B.: Proc. Natl. Acad. Sci. U. S. **2**, 69–73 (1916).

(359) JOHNSON, T. B.: J. Am. Chem. Soc. **61**, 2485–7 (1939).
(360) JOHNSON, T. B., AND BATES, J. S.: J. Am. Chem. Soc. **37**, 383–5 (1915).
(361) JOHNSON, T. B., AND BATES, J. S.: J. Am. Chem. Soc. **38**, 1087–98 (1916).
(362) JOHNSON, T. B., AND BENGIS, R.: J. Am. Chem. Soc. **34**, 1054–61 (1912).
(363) JOHNSON, T. B., AND BENGIS, R.: J. Am. Chem. Soc. **34**, 1061–6 (1912).
(364) JOHNSON, T. B., AND BENGIS, R.: J. Am. Chem. Soc. **35**, 1605–6 (1913).
(365) JOHNSON, T. B., AND BENGIS, R.: J. Am. Chem. Soc. **35**, 1606–17 (1913).
(366) JOHNSON, T. B., AND BRAUTLECHT, C.: J. Am. Chem. Soc. **33**, 1531–8 (1911).
(367) JOHNSON, T. B., AND BRAUTLECHT, C.: J. Biol. Chem. **12**, 175–96 (1912).
(368) JOHNSON, T. B., AND CHERNOFF, L. H.: J. Am. Chem. Soc. **34**, 1208–13 (1912).
(369) JOHNSON, T. B., AND GUEST, H. H.: Am. Chem. J. **47**, 242–51 (1912).
(370) JOHNSON, T. B., AND GUEST, H. H.: Am. Chem. J. **48**, 103–11 (1912).
(371) JOHNSON, T. B., AND HADLEY, S. E.: J. Am. Chem. Soc. **37**, 171–77 (1915).
(372) JOHNSON, T. B., AND HAHN, D. A.: J. Am. Chem. Soc. **39**, 1255–66 (1917).
(373) JOHNSON, T. B., AND HEMINGWAY, E. H.: J. Am. Chem. Soc. **38**, 1550–57 (1916).
(374) JOHNSON, T. B., HILL, A. J., AND BAILEY, B. H.: J. Am. Chem. Soc. **37**, 2406–16 (1915).
(375) JOHNSON, T. B., HILL, A. J., AND KELSEY, E. B.: J. Am. Chem. Soc. **42**, 1711–20 (1920).
(376) JOHNSON, T. B., AND HOFFMAN, C.: Am. Chem. J. **47**, 20–7 (1912).
(377) JOHNSON, T. B., AND NICOLET, B. H.: J. Am. Chem. Soc. **33**, 1973–8 (1911).
(378) JOHNSON, T. B., AND NICOLET, B. H.: Am. Chem. J. **47**, 459–75 (1912).
(379) JOHNSON, T. B., AND NICOLET, B. H.: J. Am. Chem. Soc. **34**, 1048–54 (1912).
(380) JOHNSON, T. B., AND NICOLET, B. H.: Am. Chem. J. **49**, 197–204 (1913).
(381) JOHNSON, T. B., AND NICOLET, B. H.: J. Am. Chem. Soc. **36**, 355–64 (1914).
(382) JOHNSON, T. B., AND O'BRIEN, W. B.: J. Biol. Chem. **12**, 205–13 (1912).
(383) JOHNSON, T. B., PFAU, G. M., AND HODGE, W. W.: J. Am. Chem. Soc. **34**, 1041–8 (1912).
(384) JOHNSON, T. B., AND RENFREW, A. G.: J. Am. Chem. Soc. **47**, 240–5 (1925).
(385) JOHNSON, T. B., AND SCOTT, W. M.: J. Am. Chem. Soc. **35**, 1130–6 (1913).
(386) JOHNSON, T. B., AND SCOTT, W. M.: J. Am. Chem. Soc. **35**, 1136–43 (1913).
(387) JOHNSON, T. B., AND SCOTT, W. M.: J. Am. Chem. Soc. **37**, 1846–56 (1915).
(388) JOHNSON, T. B., AND SCOTT, W. M.: J. Am. Chem. Soc. **37**, 1856–63 (1915).
(389) JOHNSON, T. B., AND SHEPARD, N. A.: J. Am. Chem. Soc. **36**, 1735–42 (1914).
(390) JOHNSON, T. B., AND TICKNOR, A. A.: J. Am. Chem. Soc. **40**, 636–46 (1918).
(391) JOHNSON, T. B., AND WRENSHALL, R.: J. Am. Chem. Soc. **37**, 2133–44 (1915).
(392) JONES, L. W., AND MAJOR, R. T.: J. Am. Chem. Soc. **52**, 1078–85 (1930).
(393) JONES, T. D., AND JACOBS, J. L.: J. Am. Med. Assoc. **99**, 18–21 (1932).
(394) JONGKEES, W. J. A.: Rec. trav. chim. **27**, 287–326 (1908).
(395) KAMIN, C. G.: U. S. patent 2,441,360 (May 11, 1948); Chem. Abstracts **42**, 5271 (1948).
(396) KARABINOS, J. V., AND SZABO, J. L.: J. Am. Chem. Soc. **66**, 649–50 (1944).
(397) KARRER, P., AND EHRENSTEIN, M.: Helv. Chim. Acta **9**, 323–31 (1926).
(398) KEACH, D. T.: J. Am. Chem. Soc. **55**, 2979–81 (1933).
(399) KIMBALL, O. P.: J. Am. Med. Assoc. **112**, 1244–5 (1939).
(400) KLASON, P.: Ofv. Kongl. Vet. Akad. **1890**, 87; Chem. Zentr. **1890, II**, 344.
(401) KLOSTERMAN, H. J., AND PAINTER, E. P.: J. Am. Chem. Soc. **69**, 2009–10 (1947).
(402) KODAMA, S.: J. Tokyo Chem. Soc. **41**, 951–65 (1920); Chem. Abstracts **15**, 1511 (1921).
(403) KODAMA, S.: J. Chem. Soc. Japan **42**, 1005–17 (1921); Chem. Abstracts **16**, 1933 (1922).
(404) KOENIGS, E., AND MYLO, B.: Ber. **41**, 4427–43 (1908).
(405) KOLBE, H.: Ber. **3**, 183–7 (1870).
(406) KOLBE, H.: J. prakt. Chem. [2] **1**, 134–41 (1870).
(407) KOMATSU, S.: Mem. Coll. Sci. Eng. Kyoto Imp. Univ. **3**, 1–12 (1911).
(408) KOMATSU, S.: Mem. Coll. Sci. Kyoto Imp. Univ. **1**, 69–79 (1915).
(409) KOSSEL, A.: Ber. **24**, 4145–56 (1891).

(410) KOTAKE, M.: Sci. Papers Inst. Phys. Chem. Research (Tokyo) **6**, 61–65 (1927).
(411) KOZÁK, J., AND MUSIAL, L.: Bull. intern. acad. polonaise **1930A**, 432–8.
(412) KOZELKA, F. L., AND HINE, C. H.: J. Pharmacol. **72**, 276–9 (1941).
(413) KUHN, B.: Ber. **17**, 2880–5 (1884).
(414) KUOFEL, P. K., AND LEHMANN, G.: J. Pharmacol. **76**, 194–201 (1942).
(415) LANDOLT, H.: Thesis, "Zur Kenntnis der Hydantoine," Zurich, 1930.
(416) LANGE, A.: Ber. **12**, 595–99 (1879).
(417) LAW, G. H., AND JOHNSON, T. B.: J. Am. Chem. Soc. **52**, 3623–7 (1930).
(418) LEHMANN, F.: Ber. **34**, 366–77 (1901).
(419) LEUCHS, H., AND GEIGER, W.: Ber. **39**, 2644–9 (1906).
(420) LEUTHARDT, F., AND BRUNNER, R.: Helv. Chim. Acta **30**, 964–5 (1947).
(421) LEWIS, H. B.: J. Biol. Chem. **13**, 347–56 (1912).
(422) LEWIS, H. B.: J. Biol. Chem. **14**, 245–56 (1913).
(423) LI, L., LIN, K., HUANG, Y., AND KANG, S.: J. Chinese Chem. Soc. **9**, 1–13 (1942); Chem. Abstracts **38**, 334 (1944).
(424) LIEB, V. A.: Dissertation, Munich, 1933.
(425) LIEBERMANN, C., AND LANGE, A.: Ber. **12**, 1588–95 (1879).
(426) LIEBERMANN, C., AND LANGE, A.: Ann. **207**, 123–37 (1881).
(427) LINGO, S. P., AND HENZE, H. R.: J. Am. Chem. Soc. **61**, 1574–6 (1939).
(428) LINGO, S. P., AND HENZE, H. R.: J. Am. Chem. Soc. **61**, 2029–32 (1939).
(429) LINSKER, F., AND EVANS, R. L.: J. Am. Chem. Soc. **68**, 947–8 (1946).
(430) LIPPICH, F.: Ber. **39**, 2953–6 (1906).
(431) LIPPICH, F.: Ber. **41**, 2953–74 (1908).
(432) LIPPICH, F.: Ber. **41**, 2974–83 (1908).
(433) LIPPICH, F.: Z. physiol. Chem. **90**, 442–88 (1914).
(434) LIPPMANN, E. O. VON: Ber. **29**, 2645–54 (1896).
(435) LITZINGER, A.: J. Am. Chem. Soc. **56**, 673–7 (1934).
(436) LIVAK, J. E., BRITTON, E. C., VANDERWEELE, J. C., AND MURRAY, M. F.: J. Am. Chem. Soc. **67**, 2218–20 (1945).
(437) LIVAK, J. E., AND MURRAY, M. F.: U. S. patent 2,435,399 (February 3, 1948); Chem. Abstracts **42**, 4613 (1948).
(438) LOCQUIN, R., AND CERCHEZ, V.: Compt. rend. **188**, 177–9 (1929).
(439) LOCQUIN, R., AND CERCHEZ, V.: Bull. soc. chim. [4] **49**, 309–18 (1931).
(440) LONG, L. M.: U. S. patents 2,404,509–10 (July 23, 1946); Chem. Abstracts **40**, 6095 (1946).
(441) LONG, L. M.: J. Am. Chem. Soc. **68**, 2159–61 (1946).
(442) LONG, L. M., MILLER, C. A., AND CHEN, G.: J. Am. Chem. Soc. **71**, 669–70 (1949).
(443) LONG, L. M., MILLER, C. A., AND TROUTMAN, H. D.: J. Am. Chem. Soc. **70**, 900–3 (1948).
(444) LUMIÈRE, A., LUMIÈRE, L., AND BARBIER, H.: Bull. soc. chim. [3] **35**, 123–6 (1906).
(445) LUMIÈRE, A., AND PERRIN, F.: Bull. soc. chim. [4] **35**, 1022–6 (1924).
(446) MCCOWN, W. H., AND HENZE, H. R.: J. Am. Chem. Soc. **64**, 689–90 (1942).
(447) MCKEE, R. L., AND HENZE, H. R.: J. Am. Chem. Soc. **66**, 2020–3 (1944).
(448) MCLEAN, M. J., AND SEEGER, D. R.: J. Am. Chem. Soc. **62**, 1416–19 (1940).
(449) MCMEEKIN, T. L., COHN, E. J., AND WEARE, J. H.: J. Am. Chem. Soc. **57**, 626–33 (1935).
(450) MCMEEKIN, T. L., COHN, E. J., AND WEARE, J. H.: J. Am. Chem. Soc. **58**, 2173–81 (1936).
(451) MAGEE, J. W., AND HENZE, H. R.: J. Am. Chem. Soc. **60**, 2148–51 (1938).
(452) MAJIMA, R., AND KOTAKE, M.: Ber. **55**, 3859–65 (1922).
(453) MALY, R.: Ann. **168**, 133–9 (1873).
(454) MARCKWALD, W., NEUMARK, M., AND STELZNER, R.: Ber. **24**, 3278–98 (1891).
(455) MARSH, D., AND LAZZELL, C. L.: J. Am. Chem. Soc. **62**, 1306 (1940).
(456) MARTELL, A. E., AND HERBST, R. M.: J. Org. Chem. **6**, 878–87 (1941).

(457) MATIGNON, C.: Ann. chim. phys. [6] **28**, 70–125 (1893); Chem. Zentr. **1893**, 344–6.
(458) MELTON, J. W., AND HENZE, H. R.: J. Am. Chem. Soc. **69**, 2018–19 (1947).
(459) MENTZER, C., AND BILLET, D.: Compt. rend. **228**, 402–4 (1949).
(460) MERRITT, H. H., AND FOSTER, A.: Am. J. Med. Sci. **200**, 541–4 (1940).
(461) MERRITT, H. H., AND PUTNAM, T. J.: J. Am. Med. Assoc. **111**, 1068–73 (1938).
(462) MERRITT, H. H., PUTNAM, T. J., AND BYWATER, W. G.: J. Pharmacol. **84**, 67–7 (1945).
(463) MILLER, E. J., AND ROBSON, W.: J. Chem. Soc. **1938**, 1910–12.
(464) MITCHELL, H. K., AND NYC, J. F.: J. Am. Chem. Soc. **69**, 674–7 (1947).
(465) MOREL, A.: Compt. rend. **143**, 119–21 (1906).
(466) MORGAN, W. T. J.: J. Chem. Soc. **1926**, 79–84.
(467) MOSSINI, A., AND GUERCI, R.: Boll. chim. farm. **80**, 343–6 (1941); Chem. Abstracts **37**, 3756 (1943).
(468) MOUNEYRAT, A.: Ber. **33**, 2393–6 (1900).
(469) MOZINGO, R., WOLF, D. E., HARRIS, S. A., AND FOLKERS, K.: J. Am. Chem. Soc. **65**, 1013–16 (1943).
(470) MULDER, E.: Z. Chem. [N. F.] **7**, 693 (1871); Chem. Zentr. **1872**, 500.
(471) MULDER, E.: Ber. **8**, 1261–7 (1875).
(472) NAMJOSHI, V. G., AND DUTT, S.: J. Indian Chem. Soc. **8**, 241–6 (1931).
(473) NENCKI, M.: Ber. **6**, 598–600 (1873).
(474) NEUBAUER, C.: Ann. **137**, 288–98 (1866).
(475) NEUBERG, C., AND MANASSE, A.: Ber. **38**, 2359–66 (1905).
(476) NEUBERG, C., AND ROSENBERG, E.: Biochem. Z. **5**, 456–60 (1907).
(477) NICOLET, B. H.: J. Am. Chem. Soc. **37**, 2753–6 (1915).
(478) NICOLET, B. H.: J. Am. Chem. Soc. **52**, 1192–5 (1930).
(479) NICOLET, B. H.: J. Biol. Chem. **88**, 395–401 (1930).
(480) NICOLET, B. H.: Science **71**, 589–90 (1930).
(481) NICOLET, B. H.: J. Biol. Chem. **99**, 429–33 (1933).
(482) NICOLET, B. H., AND CAMPBELL, E. D.: J. Am. Chem. Soc. **50**, 1155–60 (1928).
(483) NIEMANN, C., LEWIS, R. N., AND HAYS, J. T.: J. Am. Chem. Soc. **64**, 1678–82 (1942).
(484) NIENBERG, H., AND TAUBOCK, K.: Z. physiol. Chem. **250**, 80–6 (1937).
(485) NOVELLI, A.: Anales asoc. quím. argentina **29**, 83–7 (1941); Chem. Abstracts **35**, 6576 (1941).
(486) NOVELLI, A.: Anales asoc. quím. argentina **29**, 181–4 (1941); Chem. Abstracts **36**, 2846 (1942).
(487) NOVELLI, A., LUGONES, Z. M., AND VELASCO, P.: Anales asoc. quím. argentina **30**, 225–31 (1942); Chem. Abstracts **37**, 2820 (1943).
(488) NOVELLI, A., AND ZWAIG, M. J.: Anales asoc. quím. argentina **32**, 89–101 (1944); Chem. Abstracts **39**, 1409 (1945).
(489) NYC, J. F., AND MITCHELL, H. K.: J. Am. Chem. Soc. **69**, 1382–4 (1947).
(490) PAAL, C.: Ber. **27**, 974–9 (1894).
(491) PAAL, C., AND GANSER, F.: Ber. **28**, 3227–34 (1895).
(492) PAAL, C., AND ZITELMANN, G.: Ber. **36**, 3337–45 (1903).
(493) PARKE, DAVIS AND COMPANY: British patent 526,024 (September 9, 1940); Chem. Abstracts **35**, 6980 (1941).
(494) PATTEN, A. J.: Z. physiol. Chem. **39**, 350–5 (1903).
(495) PAULY, H., AND SAUTER, H.: Ber. **63**, 2063–9 (1930).
(496) PENDSE, G. P., AND DUTT, S.: J. Indian Chem. Soc. **7**, 953–6 (1930).
(497) PETERS, F. T.: U. S. patent 2,422,255 (June 17, 1947); Chem. Abstracts **41**, 5266 (1947).
(498) PFEIFFER, P., AND DIEBOLD, A.: J. prakt. Chem. **148**, 24–34 (1937).
(499) PFEIFFER, P., AND EPLER, H.: Ann. **545**, 263–86 (1940).
(500) PFEIFFER, P., AND HEINRICH, E.: J. prakt. Chem. **146**, 105–12 (1936).
(501) PFEIFFER, P., AND HEINRICH, E.: J. prakt. Chem. **147**, 93–8 (1936).
(502) PFEIFFER, P., AND HEINRICH, E.: J. prakt. Chem. **156**, 241–59 (1940).

(503) PFEIFFER, P., AND HOYER, H.: J. prakt. Chem. **138**, 69–79 (1933).
(504) PFEIFFER, P., AND SIMONS, H.: J. prakt. Chem. **160**, 83–94 (1942).
(505) PHILLIPS, A. P.: J. Am. Chem. Soc. **67**, 744–8 (1945).
(506) PIAUX, L.: Bull. soc. chim. [4] **37**, 311–26 (1925).
(507) PICKETT, L. W., AND MCLEAN, M.: J. Am. Chem. Soc. **61**, 423–5 (1939).
(508) PIERSON, E., GIELLA, M., AND TISHLER, M.: J. Am. Chem. Soc. **70**, 1450–1 (1948).
(509) PINNER, A.: Ber. **21**, 2320–9 (1888).
(510) PINNER, A., AND LIFSCHUTZ, J.: Ber. **20**, 2351–8 (1887).
(511) PINNER, A., AND SPILKER, A.: Ber. **22**, 685–98 (1889).
(512) POPE, W. J., AND WHITWORTH, J. B.: Chemistry & Industry **49**, 748 (1930).
(513) POWELL, S. G., AND HAGEMANN, F.: J. Am. Chem. Soc. **66**, 372–6 (1944).
(514) POZZI-ESCOT, E.: Anales quím. labs. invest. cient. e ind. E. Pozzi-Escot (Peru) Oct., **1943**, 35–6; Chem. Abstracts **38**, 1479 (1944).
(515) PUTNAM, T. J., AND MERRITT, H. H.: Science **85**, 525–6 (1937).
(516) RAIZISS, G. W., CLEMENCE, L. W., AND FREIFELDER, M.: J. Am. Chem. Soc. **63**, 2739–40 (1941).
(517) RAIZISS, G. W., CLEMENCE, L. W., AND FREIFELDER, M.: U. S. patent 2,384,964 (September 18, 1945); Chem. Abstracts **40**, 176 (1946).
(518) READ, W. T.: J. Am. Chem. Soc. **44**, 1746–55 (1922).
(519) RENFREW, A. G., AND JOHNSON, T. B.: J. Am. Chem. Soc. **51**, 254–9 (1929).
(520) RENFREW, A. G., AND JOHNSON, T. B.: J. Am. Chem. Soc. **51**, 1784–9 (1929).
(521) RHEINECK, H.: Ann. **134**, 219–28 (1865).
(522) RIGLER, N. E., AND HENZE, H. R.: J. Am. Chem. Soc. **58**, 474–7 (1936).
(523) RINKES, I. J.: Rec. trav. chim. **46**, 268–77 (1927).
(524) ROBSON, W.: J. Biol. Chem. **62**, 495–514 (1924).
(525) ROEDER, F.: Therap. Monatsh. **33**, 54–63 (1919); Chem. Zentr. **1919, II**, 529.
(526) ROGERS, A. O.: U. S. patent 2,391,799 (December 25, 1945); Chem. Abstracts **40**, 1876 (1946).
(527) ROGERS, A. O.: U. S. patent 2,392,505 (January 8, 1946); Chem. Abstracts **40**, 2467 (1946).
(528) ROGERS, A. O.: U. S. patent 2,398,598 (April 16, 1946); Chem. Abstracts **40**, 3773 (1946).
(529) ROGERS, A. O.: U. S. patent 2,398,599 (April 16, 1946); Chem. Abstracts **40**, 3773 (1946).
(530) ROGERS, A. O.: U. S. patent 2,404,096 (July 16, 1946); Chem. Abstracts **40**, 6096 (1946).
(531) ROGERS, B. G., AND HENZE, H. R.: J. Am. Chem. Soc. **62**, 1758–60 (1940).
(532) ROGERS, B. G., AND HENZE, H. R.: J. Am. Chem. Soc. **63**, 2190–1 (1941).
(533) ROMO, J. A.: Quimica (Mex.) **2**, No. 2, 8–9 (1944); Chem. Abstracts **38**, 5214 (1944).
(534) ROSENMUND, K. W., AND HERRMANN, F.: Ber. deut. pharm. Ges. **22**, 96–103 (1912); Chem. Zentr. **1912, I**, 1793.
(535) RUBIN, N., AND DAY, A. R.: J. Org. Chem. **5**, 54–60 (1940).
(536) RUDDER, B. DE: Klin. Wochschr. **5**, 1522–3 (1926); Chem. Abstracts **20**, 3732 (1926).
(537) RUDY, H., AND CRAMER, K. E.: Ber. **72**, 728–44 (1939).
(538) RUHEMANN, S., AND CUNNINGTON, R. V.: J. Chem. Soc. **75**, 954–63 (1899).
(539) RUHEMANN, S., AND STAPLETON, H. E.: J. Chem. Soc. **77**, 239–51 (1900).
(540) RUPE, H., AND KNUP, E.: Helv. Chim. Acta **10**, 299–309 (1927).
(541) RUSKIN, S. L.: U. S. patent 2,013,717 (September 10, 1935); Chem. Abstracts **29**, 7021 (1935).
(542) RUSKIN, S. L.: U. S. patent 2,407,686 (September 17, 1946); Chem. Abstracts **41**, 1393 (1947).
(543) RUSKIN, S. L., AND PFALZ, M.: J. Am. Chem. Soc. **60**, 1471–2 (1938).
(544) SAH, P. P. T., AND LIN, T.: Science Repts. Natl. Tsing Hua Univ., Series A, **4**, 31–3 (1937); Chem. Abstracts **31**, 6203 (1937).

(545) SAKAMI, W., AND WILSON, D. W.: J. Biol. Chem. **154**, 215–222 (1944).
(546) SALKOWSKI, E.: Ber. **7**, 116–19 (1874).
(547) SALMON, M. R., AND KOZLOWSKI, A. Z.: J. Am. Chem. Soc. **67**, 2270–1 (1945).
(548) SAVARD, K., RICHARDSON, E. M., AND GRANT, G. A.: Can. J. Research **24B**, 28–36 (1946).
(549) SCHAAF, F., AND LABOUCHÈRE, A.: Helv. Chim. Acta **7**, 357–63 (1924).
(550) SCHLACH, P., AND KUMPF, W.: Z. physiol. Chem. **154**, 125–70 (1926).
(551) SCHÖBERL, A., AND HORNUNG, T.: Ann. **534**, 210–25 (1938).
(552) SCHROEDER, H. E.: U. S. patent 2,416,667 (March 4, 1947); Chem. Abstracts **41**, 2930 (1947).
(553) SCHULTZEN, O.: Ber. **5**, 578–81 (1872).
(554) SCHULZE, E., AND BARBIERI, J.: Ber. **14**, 1834 (1881).
(555) SCHWEBEL, P.: Ber. **10**, 2045–50 (1877).
(556) SCHWEBEL, P.: Ber. **11**, 1128–31 (1878).
(557) SCOTT, J. R., AND COHEN, J. B.: J. Chem. Soc. **119**, 664–72 (1921).
(558) SEEGER, D. R., AND MACMILLAN, A.: J. Am. Chem. Soc. **64**, 1687–91 (1942).
(559) SEEKLES, L.: Rec. trav. chim. **46**, 77–84 (1927).
(560) SEIKEL, M. K.: J. Am. Chem. Soc. **59**, 436–9 (1937).
(561) SHABICA, A. C., HOWE, E. E., ZIEGLER, J. B., AND TISHLER, M.: J. Am. Chem. Soc. **68**, 1156–7 (1946).
(562) SHCHUKINA, M. N.: J. Gen. Chem. (U.S.S.R.) **10**, 1108–12 (1940); Chem. Abstracts **35**, 4022 (1941).
(563) SHEMIN, D., AND HERBST, R. M.: J. Am. Chem. Soc. **61**, 2471–2 (1939).
(564) SHIPLE, G. J., AND SHERWIN, C. P.: J. Biol. Chem. **55**, 671–86 (1923).
(565) SIEMONSON, L.: Ann. **333**, 101–41 (1904).
(566) SJOLLEMA, B., AND SEEKLES, L.: Rec. trav. chim. **45**, 232–5 (1926).
(567) SKITA, A., AND LEVI, R.: Ber. **41**, 2925–37 (1908).
(568) SLOTTA, K., BEHNISCH, R., AND SZYSZKA, G.: Ber. **67**, 1529–35 (1934).
(569) SLOTTA, K. H., AND SOREMBA, K.-H.: Ber. **69**, 566–72 (1936).
(570) SNYDER, H. R., HOWE, E. E., CANNON, G. W., AND NYMAN, M. A.: J. Am. Chem. Soc. **65**, 2211–14 (1943).
(571) SOBOTKA, H.: French patent 736,319 (September 5, 1931); Chem. Abstracts **27**, 1362 (1933).
(572) SOBOTKA, H.: U. S. patent 1,861,458 (June 7, 1932); Chem. Abstracts **26**, 4133 (1932).
(573) SOBOTKA, H., HOLZMAN, M. F., AND KAHN, J.: J. Am. Chem. Soc. **54**, 4697–702 (1932).
(574) SOBOTKA, H., PECK, S. M., AND KAHN, J.: J. Pharmacol. **47**, 209–15 (1933).
(575) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patent 171,872 (December 1, 1934); Chem. Abstracts **29**, 5604 (1935).
(576) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patent 174,461 (April 1, 1935); Chem. Abstracts **30**, 248 (1936).
(577) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: French patent 780,461 (April 26, 1935); Chem. Abstracts **29**, 5995 (1935).
(578) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patents 179,693–5 (December 2, 1935); Chem. Abstracts **30**, 3592 (1936).
(579) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patent 206,688 (December 1, 1939); Chem. Abstracts **35**, 3104 (1941).
(580) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: British patent 530,883 (December 24, 1940); Chem. Abstracts **36**, 1192 (1942).
(581) SPEER, R. J., AND HENZE, H. R.: J. Am. Chem. Soc. **61**, 3376–7 (1939).
(582) SPIELMAN, M. A.: U. S. patent 2,305,501 (December 15, 1942); Chem. Abstracts **37**, 3108 (1943).
(583) SPRINSON, D. B., AND CHARGAFF, E.: J. Biol. Chem. **164**, 417–32 (1946).
(584) SPURLOCK, J. J.: U. S. patent 2,366,221 (January 2, 1945); Chem. Abstracts **39**, 1736 (1945).

(585) SPURLOCK, J. J., AND HENZE, H. R.: J. Am. Chem. Soc. **60**, 3005–7 (1938).
(586) STEWART, W. D.: U. S. patent 2,430,591 (November 11, 1947); Chem. Abstracts **42**, 2810 (1948).
(587) STRECKER, A.: Ann. **155**, 177–85 (1870).
(588) STUCKEY, R. E.: Nature **160**, 189–90 (1947).
(589) STUCKEY, R. E.: J. Chem. Soc. **1947**, 331–4.
(590) SZABO, J. L., AND KARABINOS, J. V.: J. Am. Chem. Soc. **66**, 650–1 (1944).
(591) SZEKI, T., AND LAKOS, E.: Acta Sci. Univ. Francisco Iosephinae, Acta Chem., Mineral., Physica **I**, 157–66 (1929); Chem. Abstracts **25**, 2986 (1931).
(592) TAFEL, J., AND REINDL, L.: Ber. **34**, 3286–91 (1901).
(593) TAMARI, K.: J. Agr. Chem. Soc. Japan **17**, 321–35 (1941); Chem. Abstracts **41**, 4545 (1947).
(594) TAMAYO, M. L., AND GARRIDO, J.: Anales fís. y quím. (Madrid) **43**, 54–9 (1947); Chem. Abstracts **41**, 4056 (1947).
(595) TAMAYO, M. L., AND GARRIDO, J.: Anales fís. y quím. (Madrid) **43**, 1011–6 (1947); Chem. Abstracts **42**, 2893 (1948).
(596) TCHOUBAR, B.: Ind. parfum. **2**, 193–5 (1947); Chem. Abstracts **41**, 7668 (1947).
(597) TEAGUE, P. C.: J. Am. Chem. Soc. **69**, 714 (1947).
(598) THOMPSON, T. J., BEDELL, H. L., AND BUFFETT, G. M.: J. Am. Chem. Soc. **47**, 874–6 (1925).
(599) TIFFENEAU, M., TCHOUBAR, B., SAIASLAMBERT, MME., AND LETELLIER-DUPRE, MME.: Bull. soc. chim. France **1947**, 445–50.
(600) TIFFENEAU, R., AND BEAUVALLET, M.: Presse méd. **51**, 417–8 (1943); Chem. Zentr. **1943, II**, 1894.
(601) TOMISEK, A. J.: J. Am. Chem. Soc. **71**, 1138 (1949).
(602) TRAUBE, W., AND HOFFA, E.: Ber. **31**, 162–9 (1898).
(603) TROPP, C.: Ber. **61**, 1431–9 (1928).
(604) TRÜBSBACH, P. A.: Z. physik. Chem. **16**, 708–28 (1895).
(605) URECH, F.: Ber. **4**, 526–7 (1871).
(606) URECH, F.: Ber. **5**, 643 (1872).
(607) URECH, F.: Ann. **164**, 255–279 (1872).
(608) URECH, F.: Ann. **165**, 99–103 (1873).
(609) URECH, F.: Ber. **6**, 1113–17 (1873).
(610) VAN VEAN, A. G., AND HYMAN, A. J.: Rec. trav. chim. **54**, 493–501 (1935).
(611) VOLHARD, J.: J. prakt. Chem. **9**, 6–30 (1874).
(612) VOLHARD, J.: Ann. **166**, 383–4 (1873).
(613) WADA, M.: Biochem. Z. **260**, 47–51 (1933).
(614) WADA, M.: Proc. Imp. Acad. (Tokyo) **9**, 43–6 (1933).
(615) WADA, M.: Proc. Imp. Acad. (Tokyo) **10**, 17–20 (1934).
(616) WADA, M., AND HAYAMA, N.: Proc. Imp. Acad. (Tokyo) **9**, 305–8 (1933).
(617) WALKER, J. F.: U. S. patent 2,417,999 (March 25, 1947); Chem. Abstracts **41**, 4511 (1947).
(618) WALKER, J. F.: U. S. patent 2,418,000 (March 25, 1947); Chem. Abstracts **41**, 4512 (1947).
(619) WARE, E.: J. Am. Chem. Soc. **60**, 2653–6 (1938).
(620) WASER, E., AND BRAUCHLI, E.: Helv. Chim. Acta **6**, 199–205 (1923).
(621) WEIDEL, H., AND ROITHNER, E.: Monatsh. **17**, 172–90 (1896).
(622) WEITZNER, E.: Ann. **362**, 125–31 (1908).
(623) WERNECKE, E.: Deut. med. Wochschr. **42**, 1193–4 (1916); Chem. Abstracts **12**, 1488 (1918).
(624) WESSELY, F., AND JOHN, M.: Z. physiol. Chem. **170**, 167–82 (1927).
(625) WESSELY, F., AND MAYER, J.: Monatsh. **50**, 439–48 (1928).
(626) WEST, C. J.: J. Biol. Chem. **34**, 187–94 (1918).
(627) WHEELER, H. L., AND BRAUTLECHT, C.: Am. Chem. J. **45**, 446–51 (1911).

(628) WHEELER, H. L., AND CLAPP, S. H.: Am. Chem. J. **40**, 458–68 (1908).
(629) WHEELER, H. L., AND HOFFMAN, C.: Am. Chem. J. **45**, 368–83 (1911).
(630) WHEELER, H. L., HOFFMAN, C., AND JOHNSON, T. B.: J. Biol. Chem. **10**, 147–57 (1911).
(631) WHEELER, H. L., NICOLET, B. H., AND JOHNSON, T. B.: Am. Chem. J. **46**, 456–74 (1911).
(632) WHITNEY, W. B., AND HENZE, H. R.: J. Am. Chem. Soc. **60**, 1148–51 (1938).
(633) WIELAND, H., AND PURRMANN, R.: Ann. **544**, 163–82 (1940).
(634) WISLICENUS, J.: Ann. **165**, 103 (1873).
(635) WOOD, J. K.: J. Chem. Soc. **89**, 1831–9 (1906).
(636) YOKOYAMA, M.: J. Chem. Soc. Japan **57**, 247–50 (1936).
(637) ZEILE, K., AND MEYER, H.: Z. physiol. Chem. **252**, 101–14 (1938).
(638) ZIEF, M., AND EDSALL, J. T.: J. Am. Chem. Soc. **59**, 2245–8 (1937).